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Synthetic Applications of Nitropyridine Derivatives

Thesis for the degree of Philosophiae Doctor

Trondheim, December 2010

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ISBN 978-82-471-2468-0 (printed ver.)
ISBN 978-82-471-2469-7 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2010:238

Printed by NTNU-trykk

Preface

The presented work has been conducted at the Department of Chemistry, Norwegian University of Science and Technology (NTNU) from September 2006 to November 2010.

Several people have during the last four years made important contributions to this thesis. These efforts are described in the chapters where the work is presented and have all been greatly appreciated.

I am grateful to my supervisor Professor Anne Fiksdahl for her continuous support throughout this work. She is probably the most efficient person I know, and I have learned a lot from our collaboration. I am thankful to Professor Jan M. Bakke for his enthusiasm and honest criticism at our group meetings, and to present and previous group members for inspiring advice and discussions.

PhD Tor Erik Holt Kristensen and PhD Erik Fuglseth are acknowledged for proofreading this thesis, and for their suggestions and linguistic advice.

Present and former colleagues among the PhD students at our Department have made a friendly and social working environment which has been greatly appreciated. In particular, I would like to thank: Freddy, Ragnhild and Christian, who kept the atmosphere in the research group positive and enjoyable. Erik, who enthusiastically made sure we got weekly physical exercise and Jon Erik, who created a number of lively festivities during the years.

I would like to express my gratitude to family and friends for all their support and encouragement during my time at the university.

Finally, I am thankful to Ina for all her love and patience.

Vegar Stockmann
Trondheim, November 2010

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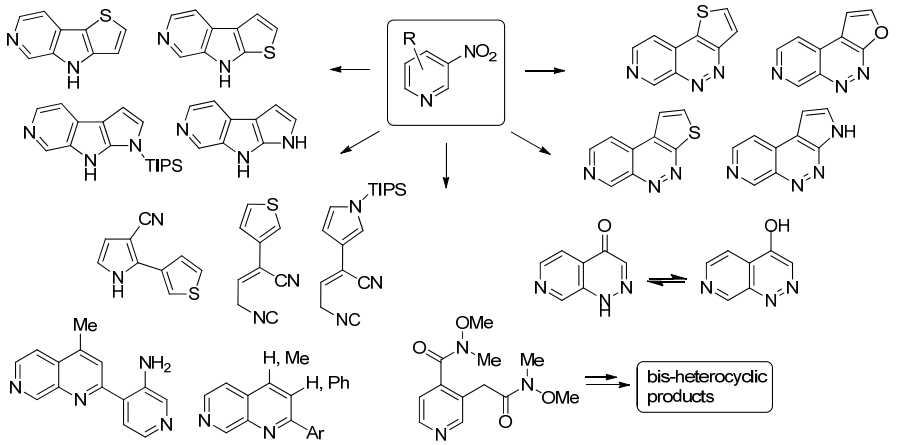
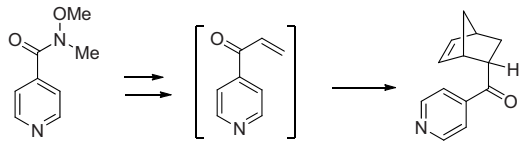
Abstract

The present work represents a continuation of the investigation of the chemistry of nitropyridine derivatives, based on the methodology for nitration of pyridines developed by Professor Jan M. Bakke and co-workers at NTNU. Nitropyridines have been utilized as substrates for the formation of novel bis- and tris-heterocyclic compounds, and new synthetic routes to fused heterocycles have been developed.



Several new β-carboline analogues and fused azacinnolines have been prepared based on a Suzuki coupling and subsequent cyclization approach. The formation of 4-isocyanobut-2-enenitrile and 3-cyanopyrrole products by ring opening and ring contraction of 3-pyridyl nitrenes, respectively, is reported. 7-Azacinnolin-4(1*H*)-one has been prepared and tautomery investigated by NMR. The general ability of appropriate pyridyl compounds to undergo Friedländer condensation to give different 1,7-naphthyridines has been demonstrated. Bis-heterocyclic products have been prepared from methyl/allylpyridylketones formed by Weinreb transformations, and a method has been developed to allow for the preparation of reactive pure pyridylvinylketones to be used in further reactions, such as Diels-Alder cycloaddition reactions.



List of appended papers

Paper I

Vegar Stockmann and Anne Fiksdahl

Preparation of new pyrido[3,4-*b*]thienopyrroles and pyrido[4,3-*e*]-thienopyridazines

Tetrahedron **2008**, *64*, 7626.

Paper II

Vegar Stockmann, Kristine L. Eriksen, Anne Fiksdahl

Preparation of novel pyridine fused tris-heterocycles; pyrido[4,3-*e*]pyrrolo-/ pyrido[4,3-*e*]furano[2,3-*c*]pyridazines and pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole

Tetrahedron **2008**, *64*, 11180.

Paper III

Vegar Stockmann, Jan M. Bakke, Per Bruheim and Anne Fiksdahl

Formation of new 4-isocyanobut-2-enenitriles by thermal ring cleavage of 3-pyridyl azides

Tetrahedron **2009**, *65*, 3668.

Paper IV

Lars Kr. Hansen, Vegar Stockmann and Anne Fiksdahl

8*H*-6-Azathieno[2,3-*b*]indole

Cambridge Crystallographic Data Center. http://www.ccdc.cam.ac.uk (accessed Oct 2010), deposition number: CCDC 778181. To be published in *Acta Crystallogr.,Sect. E: Struct. Rep. Online*.

Paper V

Lars Kr. Hansen, Vegar Stockmann and Anne Fiksdahl

7-Azathieno[3,2-*c*]cinnoline

Acta Crystallogr., Sect. E: Struct. Rep. Online **2007**, *E63*, o3290.

Paper VI

Lars Kr. Hansen, Vegar Stockmann and Anne Fiksdahl

7-Azathieno[2,3-*c*]cinnoline

Acta Crystallogr., Sect. E: Struct. Rep. Online **2007**, *E63*, o3896.

Paper VII

Vegar Stockmann, Sebastian Primpke and Anne Fiksdahl

7-Azacinnolin-(1*H*)-one; preparation and NMR-studies of tautomery

J. Heterocycl. Chem. **2010**, accepted.

Paper VIII

Vegar Stockmann and Anne Fiksdahl

Synthesis of novel 1,7-naphthyridines

J. Heterocycl. Chem. **2010**, accepted.

Paper IX

Vegar Stockmann, Svein Jacob Kaspersen, Alexander Nicolaisen and Anne Fiksdahl

Studies on reactive pyridylketones formed by Weinreb transformations

J. Heterocycl. Chem. **2010**, submitted.

Abbreviations and symbols

APT	attached proton test
conc	concentrated
δ	NMR chemical shift in parts per million downfield from a standard
Δ	indicates heat
d	deuterium
2D	two-dimensional
dba	dibenzylideneacetone
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
h	hour
$h\nu$	indicates light; *h* is Planck's constant and ν is the photon frequency
HMBC	heteronuclear multiple bond correlation
HSQC	heteronuclear single quantum coherence
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
MW	micowave
n	normal
NOESY	nuclear Overhauser enhancement spectroscopy
pH	negative logarithm of hydrogen ion concentration
rt	room temperature
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	tertiary
T	temperature (in kelvins)
TBAF	tetrabutylammonium fluoride
TES	triethylsilyl
TMEDA	*N*, *N*, *N'*, *N'*-tetramethylethylenediamine
TMS	tetramethylsilane
THF	tetrahydrofurane
TIPS	triisopropylsilyl

1 Introduction

Heterocyclic compounds are of great importance in organic chemistry and biochemistry as they are predominant among the types of compounds used as drugs, veterinary products and agrochemicals.[1] Among drugs used in human medicine, a majority are heterocyclic small molecules or have heterocyclic structural components. Of the top 15 best-selling prescription drugs worldwide in the year 2009, nine were small heterocyclic molecules.[2] Accordingly, besides journals, several textbooks,[3-5] handbooks[6,7] and book series[8-10] are dedicated to the important field of heterocyclic chemistry.

1.1 Pyridines and fused ring systems

The most important six-membered heterocyclic rings contain nitrogen atoms as the hetero atoms. The parent compound of this class of molecules is pyridine (**1**), the *N*-analogue of benzene (Figure 1).[11] The pyridine ring can be fused to a second aromatic ring, forming either of the two monoazanaphthalenes, quinoline and isoquinoline. Considering other naphthalene analogues, there are six napthyridines with the nitrogens in different rings, created from two fused pyridine rings. 1,5- Naphthyridine and 2,6-naphthyridine are shown below in Figure 1. When three fused six-membered rings are considered, possibilities become numerous.

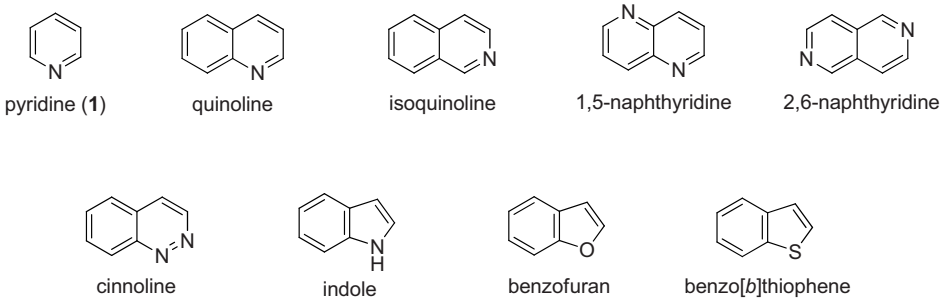


Figure 1. Pyridines and benzo-fused heteroaromatics.

Other important benzo-fused heteroaromatics, such as fused pyridazine, pyrrole, furan and thiophene, are shown above. By substituting the benzene ring with a pyridine ring, an aza analogue can be constructed e.g. azacinnoline and azaindole.

1.2 Biologically significant pyridines

Several essential vitamins are water-soluble and heterocyclic by nature. The two important pyridine-containing vitamins, B_3 (nicotinamide) and B_6 (pyridoxine) are required for the biosynthesis of nicotinamide adenine dinucleotide phosphate ($NADP^+$) and pyridoxal phosphate (PLP), respectively (Figure 2).[12] $NADP^+$ is a large complicated co-enzyme, but the crucial component for its oxidative/reductive properties is the pyridinium ring, an *N*-alkyl pyridinium salt of nicotinamide. Enzymes containing PLP have various functions, all associated with amino acids.

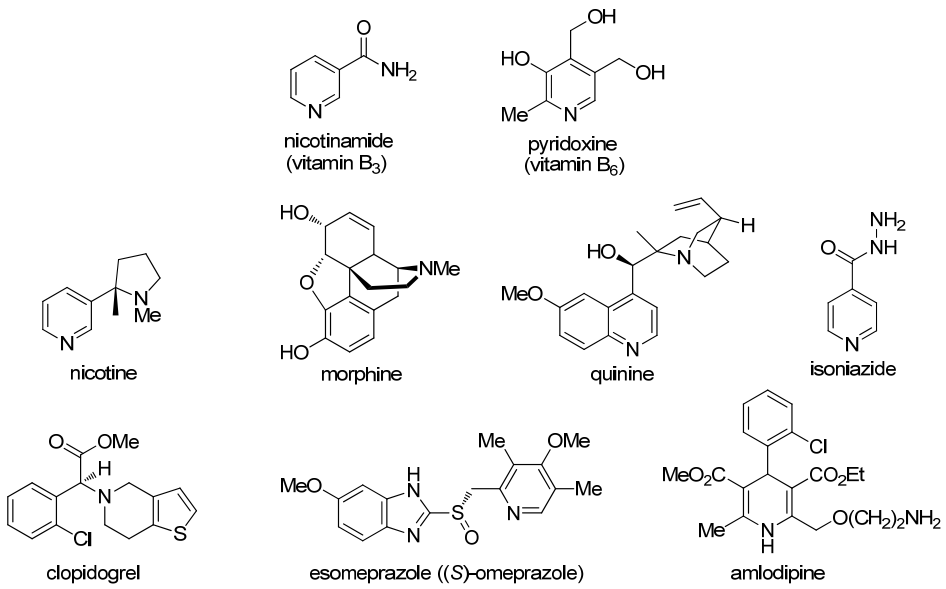


Figure 2. Biologically significant compounds containing the pyridine nucleus.

Alkaloids are naturally occurring nitrogen-containing compounds, many of which have important physiological properties.[12] Nicotine, the most active and well-known constituent of tobacco, is a toxic substance and amongst the most addictive drugs known. Many alkaloids are based on the isoquinoline or quinoline nucleus. Morphine from the opium poppy and the antimalarial quinine are typical examples.

Many biologically significant compounds used in drugs contain the pyridine nucleus.[13,14] A simple and important anti-tuberculosis drug is isoniazide. The 2nd best selling prescription drug worldwide (2009) is clopidogrel (Plavix; $9.1bn),[2] a

thienopyridine used as an antiplatelet agent to inhibit blood clots. The 3rd best selling drug is esomeprazole (Nexium; $8.2bn),[2] a proton-pump inhibitor for reduction of gastric acid. Amlodipine (Norvasc, Amlodin, Istin) is a calcium channel blocker used as an anti-hypertensive agent.[14,15]

Other applications of pyridines include their use as agrochemicals (herbicides, insecticides and fungicides), veterinary products (anthelmintics, antiparasitics and antibacterials), dyestuffs, surfactants and corrosion inhibitors.[13] Pyridines have also frequently been used as ligands for metals in organic synthesis, and are often used as chiral ligands for transition metals.[16,17] The resulting complexes act as catalysts in a variety of asymmetric transformations.

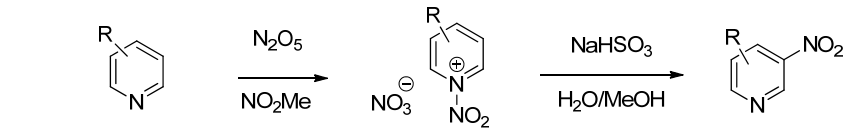
1.3 Nitration of pyridine

Due to the biological importance of pyridine derivatives, a wide range of synthetic methods for construction of the pyridine ring and formation of its derivatives have been developed.[13,18,19] Unfortunately, one of the most important methods for introducing new functionality in aromatic systems, electrophilic aromatic substitution, takes place only with great difficulty due to the nucleophilic nitrogen atom and the electron deficient character of the pyridine ring.[20]

Previously, nitration of pyridine (**1**) gave low yields of 3-nitropyridine (**2**) even under harsh conditions. Nitration methods with reagents and conditions like KNO_3 in fuming H_2SO_4 at 350 °C,[21] gaseous nitration with N_2O_4 and CO_2 at 120 °C,[22] NO_2F vapour,[23] $Ti(NO_3)_4$ in CCl_4[24] and NO_2 and ozone in CH_2Cl_2[25] all gave 3-nitropyridine (**2**) in less than 10% yield. The lack of reactivity of pyridines in electrophilic substitution has been shown to derive from their protonation due to the highly acidic conditions usually employed for nitration.[26,27] It can be estimated that pyridine itself undergoes nitration at least 10^{22} times slower than benzene.[28]

During the 1990s, Bakke and co-workers developed a nitration method for substituted pyridines (Scheme 1).[29-31] By reacting pyridine (**1**) with N_2O_5 in an organic solvent, *N*-nitropyridinium ion **3** was formed. Treatment with a solution of $NaHSO_3$ in H_2O/MeOH gave 3-nitropyridine (**2**). The synthesis of substituted nitropyridines, their subsequent reactions, as well as the detailed reaction mechanism for the nitration of pyridines have all been reviewed.[32,33]

Scheme 1

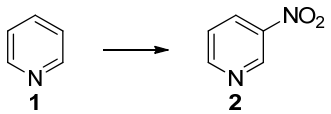


R = H: **1** **3** **2**

R = 2-CH_3, 3-CH_3, 4-CH_3, 3-Ph, 4-Ph, 4-CHO (protected), 3-$COCH_3$, 4-$COCH_3$, 4-COPh, 3-COOH, 4-COOH, 4-$COOCH_3$, 4-CN, 3-Cl, 4-$NHCOCH_3$, 4-NHCOPh, 4-$NHCO_2CH_3$

Several procedures for nitration of pyridine and substituted pyridines have been developed by continuous optimization of the reaction conditions.[29-31,34] As can be seen from Table 1, procedures D and E are more convenient, avoiding the use of liquid SO_2. In most cases the obtained yields of nitropyridines by procedure D or E were equal to or higher than those obtained by procedures A-C. Another important feature of these methods is that N_2O_5 can be produced on an industrial scale with CH_2Cl_2 as solvent.[33,31]

Table 1. Overview of procedures for nitration of pyridine.



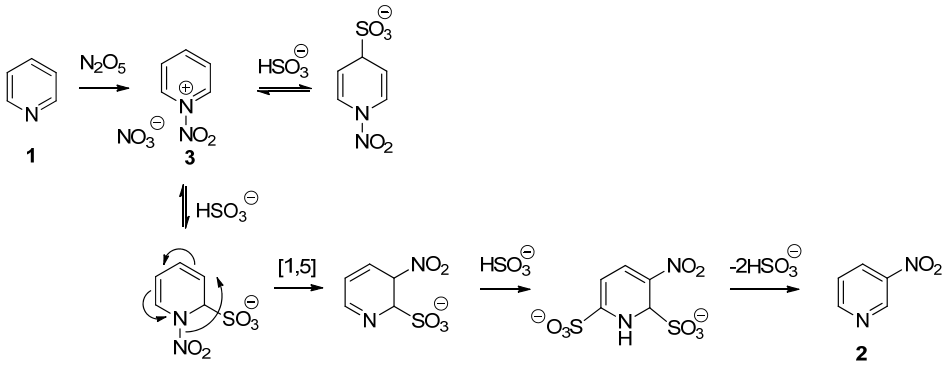
1 **2**

Procedure	Conditions	Yield (%)	Ref.
A	1) N_2O_5 in SO_2 (*l*) 2) H_2O	63	29
B	1) N_2O_5 in SO_2 (*l*)/NO_2Me 2) H_2O	58	34
C	1) N_2O_5 in SO_2 (*l*)/NO_2Me 2) $NaHSO_3/H_2O$	68	30
D	1) N_2O_5 in NO_2Me 2) $NaHSO_3/H_2O$, pH 2.5 3) HNO_3 (1 M), pH 1.0	77	30, 31
E	1) N_2O_5 in NO_2Me 2) $NaHSO_3$ in MeOH/H_2O (3:1)	67	31

Studies on the formation of nitropyridines have revealed that the reaction mechanism is not an electrophilic aromatic substitution. The first step in the reaction involves the

formation of an *N*-nitropyridinium ion **3**. Subsequently, the nitro group migrates from the 1-position to the 3-position by a [1,5] sigmatropic shift (Scheme 2).[35-37]

Scheme 2



In 2005, Katritzky, Scriven and co-workers reported that nitropyridines could be prepared by nitration of pyridines in a nitric acid/trifluoroacetic anhydride system where N_2O_5 was generated *in situ*.[38] The yields of 3-nitro products using this method were generally higher, but comparable with those of Bakke. Therefore, the mechanism of nitration was assumed to follow the same reaction pathway as proposed by Bakke.

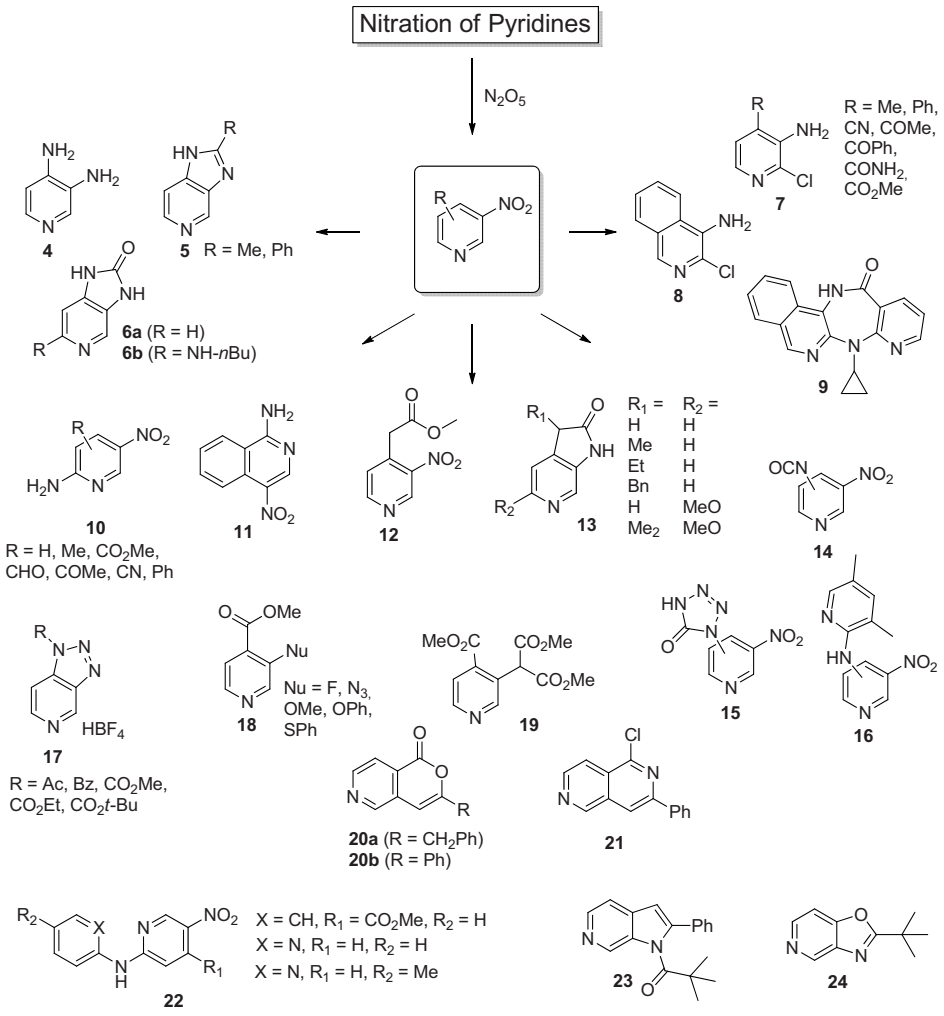
1.4 Synthetic applications of 3-nitropyridine derivatives

The new method of pyridine nitration made a number of 3-nitropyridines readily available. The chemistry of these new compounds and their applications in organic synthesis were in general unexplored, and provided new possibilities in synthetic heterocyclic chemistry. The research groups of Bakke and Fiksdahl have investigated the chemistry of nitropyridines in detail. Some of the interesting products prepared during the past 15 years are summarized in Scheme 3.

The research group of Bakke reported in 1999 the synthesis of 3,4-diaminopyridine (**4**) and imidazo[4,5-*c*]pyridines **5** by nitration of 4-acylaminopyridines.[39] 3,4-Diaminopyridine (**4**) is a drug approved for clinical use in the treatment of Lambert-Eaton myasthenic syndrome and a precursor of many biologically active heterocycles. The imidazo[4,5-*c*]pyridine structure is incorporated in a number of biologically active compounds. Nitration of 4-pyridyl carbamates allowed for an alternative route to the cyclic ureas **6a** and **6b**.[40] The cyclic urea **6a** is patented because of its antiviral and antibacterial activities, and was prepared in excellent yield by a solvent-free, "green" method developed by the Fiksdahl group in 2006.[41]

4-Substituted 3-amino-2-chloropyridines **7** are valuable compounds as further transformations can lead to a wide variety of 2, 3, 4-substituted pyridines. Riha and Bakke (2001) reported a general synthetic route to 4-substituted 3-amino-2-chloropyridines **7**, based on direct nitration of the pyridine substrate, followed by reduction and chlorination.[42] Using this method, 4-amino-3-chloroisoquinoline (**8**) was prepared and subsequently utilized in the synthesis of isoquinoline **9**, an analogue of the reverse transcriptase inhibitor nevirapine.

Scheme 3



In 2001, a report on selective vicarious nucleophilic amination of 3-nitropyridines was published.[43] Several 3-nitropyridine compounds and 4-nitroisoquinoline were aminated in the 6-position (C1 of 4-nitroisoquinoline) to give substituted 2-amino-5-nitropyridines **10** and 1-amino-4-nitroisoquinoline (**11**). 2,5-Substituted pyridines are present in many pharmaceuticals and would be useful starting compounds for the synthesis of other physiologically active compounds. Nucleophilic alkylations of 3-nitropyridines were also investigated.[44] One specific alkyl substituted product **12** proved to be a valuable starting compound for the synthesis of substituted 6-azaindoles **13**, opening a new route to a series of compounds with potential biological activity.[45]

The research group of Fiksdahl reported in 2005 the first preparation of 3-nitropyridyl isocyanates **14** and discussed their stability and use for synthetic purposes.[46] The application of nitropyridyl isocyanates in 1,3-dipolar cycloaddition reactions for the synthesis of the new compounds **15** and **16** was then described.[47]

N-acyl- and *N*-alkoxycarbonyl triazolopyridines **17** have been readily prepared in four steps from 4-aminopyridine by amine protection, pyridine nitration, nitro reduction and diazotization/cyclization.[48] The *N*-acylating and *N*-alkoxycarbonylation abilities of the *N*-substituted 1,2,3-triazolo[4,5-*c*]pyridines **17** were investigated, and the presented method offers an efficient and convenient protocol for the protection of amines and amino acids.

The nitro group of methyl 3-nitropyridine-4-carboxylate has been successfully replaced by a range of heteroatom nucleophiles *via* nucleophilic aromatic substitution to give products **18**.[49,50] The alkylation of pyridine by substitution of the nitro group in methyl 3-nitro-4-pyridylcarboxylate by malonic esters has also been reported.[51] The versatility of the α-(3-pyridyl) malonic ester product **19** was demonstrated by the formation of a number of 3-alkylated pyridines and new fused bis-heterocycles, such as the *N*-heterocyclic isocoumarin analogues **20a**, **20b** and the 2,6-naphthyridine derivative **21**.

Other recent investigations include the preparation of a series of Pd^{II} complexes of *N*-aryl-2-pyridylamines **22**,[52] and the preparation of 6-azaindole **23** and oxazolopyridine **24**.[53]

The present work represents a continuation of the investigations into the chemistry of nitropyridine derivatives. The main objectives have been to utilize nitropyridine derivatives as substrate for the formation of bis- and tris-heterocyclic compounds and develop new synthetic routes to fused heterocycles.

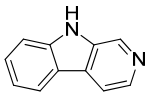
2 β-Carboline analogues and fused azacinnolines

This chapter summarizes results presented in Papers I-VI. Several people are acknowledged for their contributions to this work: Master of Technology Kristine L. Eriksen (Paper II) for her initial work on the syntheses of the pyrrolo fused β-carboline analogue and azacinnoline; Professor Lars Kristian Hansen for resolving the crystal structures of 8*H*-6-azathieno[2,3-*b*]indole (Paper IV), 7-azathieno[3,2-*c*]cinnoline (Paper V) and 7-azathieno[2,3-*c*]cinnoline (Paper VI); PhD Trygve Andreassen for technical assistance regarding the ^{15}N NMR experiments (Paper III); Associate Professor Per Bruheim for recording ESI-MS spectra of all new compounds presented in Paper III.

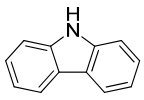
2.1 Background

β-Carbolines (**I**, Scheme 4) are a large group of natural and synthetic indole alkaloids. Some of them are widely distributed in nature, while others are artificial.[54] β-Carbolines are *N*-analogues of carbazoles (**II**), compounds that are incorporated into a number of pharmaceutical agents.

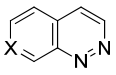
Scheme 4



I
β-carboline

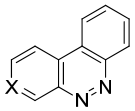


II
carbazole



IIIa; X = CH
cinnoline

IIIb; X = N
7-azacinnoline



IVa; X = CH
benzo[*c*]cinnoline

IVb; X = N
pyrido[3,4-*c*]cinnoline

The carvedilol[55] and carazolol[56] β-blockers are based on the carbazole tricyclic skeleton. Compounds containing the β-carboline ring system have been found to exhibit various biological activities such as intercalation into DNA,[57-59] affinity for $GABA_A$ receptors (often as effectively as clinically active benzodiazepines),[60,61] interaction with 5-HT_2 serotonin receptors[62] as well as imidazoline receptors[63] and inhibition of enzymes such as topoisomerase[64,65] and monoamine oxidase.[66,67] In addition, a broad spectrum of pharmacological effects of β-carbolines have been demonstrated, including antitumor,[68,69] antiviral,[70,71] antibacterial,[72,73] antiparasitic[74,75] and antithrombotic[76,77] activities, as well as hallucinogenic effects.[78] Topics of recent reviews of β-carbolines include synthesis, functionalization and transformations of β-

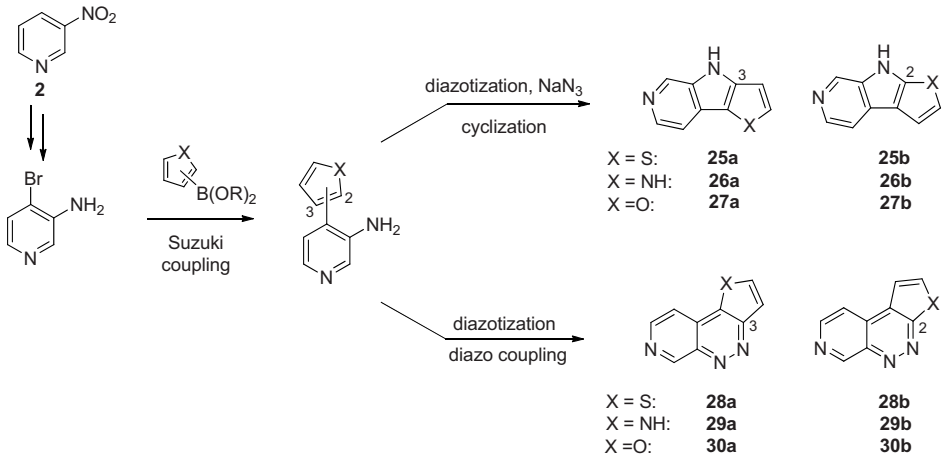
carbolines,[79] synthesis of carbolines possessing antitumor activity[80] and biochemical and pharmacological functions of β-carboline alkaloids.[81]

Cinnolines (**IIIa**, Scheme 4) are subjects to intensive biological investigations in clinical trials, due to their multidirectional biological activity.[82] The search for new cinnoline derivatives as potential drugs has increased over the last decade,[83-86] and several reviews and monographs on the synthesis and characteristics of cinnolines have been published.[87-89] Azacinnolines (**IIIb**) have been studied for their use in the treatment of Alzeimer's disease[90] and have been used for the preparation of antiviral agents.[91] A series of substituted benzo[*c*]cinnolines (**IVa**) have been found to possess herbicidal activity,[14] while others are used in dyes[92,93] or as metal surface modifiers.[94,95] The corresponding *N*-analogue, pyrido[3,4-*c*]cinnoline (**IVb**), has also been reported.[96]

2.1.1 Objective

Due to the biological activity, the therapeutic use and the general interesting properties presented above, we were interested in investigating the preparation of new, closely related, heterocyclic analogues of β-carbolines (**25-27**) and fused azocinnolines (**28-30**), as shown in Scheme 5.

Scheme 5

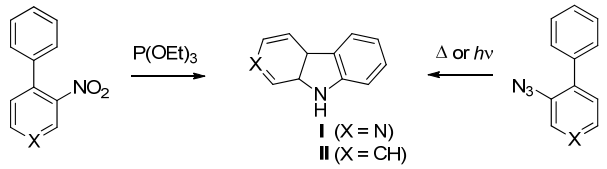


2.1.2 Synthetic strategy

In principle, two main strategies are feasible for the construction of the β-carboline system; either formation of the pyridine ring or synthesis of the pyrrole ring. Traditionally, preparation of β-carbolines has been conducted through annulations of

the pyridine ring, using the Pictet-Spengler or Bischler-Napieralski reactions.[79,97,98] Some syntheses have involved the construction of the pyrrole ring as the key step for the formation of β-carboline,[97,99] and some methods have used cycloaddition strategies.[100,101] As 3-nitropyridines have become readily available, the research group of Bakke and later the Fiksdahl group have studied an alternative pyrrole-ring construction method for the synthesis of β-carboline (**I**, Scheme 6).[102-104] Previously, carbazole (**II**) has been prepared from 1-nitro-2-phenylbenzene by treatment with $P(EtO)_3$,[105] or thermolysis[106,107]/ photolysis[108] of *o*-azidobiphenyl *via* the nitrene. Ring closures to heterocycles *via* nitrenes have recently been reviewed.[109] One of the most important nitrene-CH insertions used for cyclizations is the ring closure reaction to give an indole when starting from an arylnitrene.

Scheme 6



Unfortunately, the nature of the aryl groups may affect the cyclization reactivity adversely. While these nitrene-CH insertion reactions afford carbazoles (**II**) in high yield, the introduction of a pyridine moiety reduces the reactivity towards cyclization, and the corresponding β-carboline (**I**) is produced in significantly lower yield.[102,104] However, cyclization of 3-azido-4-phenylpyridine by thermal decomposition (*via* the nitrene) seemed to be the most promising reaction available, giving β-carboline in 14% yield.[104]

The lower yield obtained for β-carboline (**I**) when compared to carbazole (**II**) may be caused by the electron-deficient character of the pyridine moiety. To improve the reactivity and compensate for the effect of the pyridine-ring, we wanted to replace the phenyl group in the biaryl system of the precursor by more electron-rich heterocyclic groups, such as the five membered heterocycles thiophene, furan or pyrrole. This would allow us to study whether more reactive biaryl azido-intermediates could be obtained, furnishing β-carboline analogues **25**-**27** (Scheme 5). In the present work, we aimed at the preparation of the new thieno-β-carboline analogue compounds **25a** and **25b** and the pyrrolo-analogue **26b** by the 'Suzuki–intramolecular nitrene insertion' strategy.[110,111] These thieno/pyrroloazaindole products **25a**, **25b** and **26b** can be prepared from 3-amino-4-bromopyridine by palladium catalysed Suzuki cross coupling

with appropriate boronic acid derivatives followed by diazotization, azide substitution and thermolysis. This strategy would also give access to the novel fused azacinnolines **28**-**30** by intramolecular diazo coupling of the diazonium intermediate (Scheme 5). The target compounds for this study were the fused 7-azacinnolines **28a**-**b**, **29b** and **30b**.

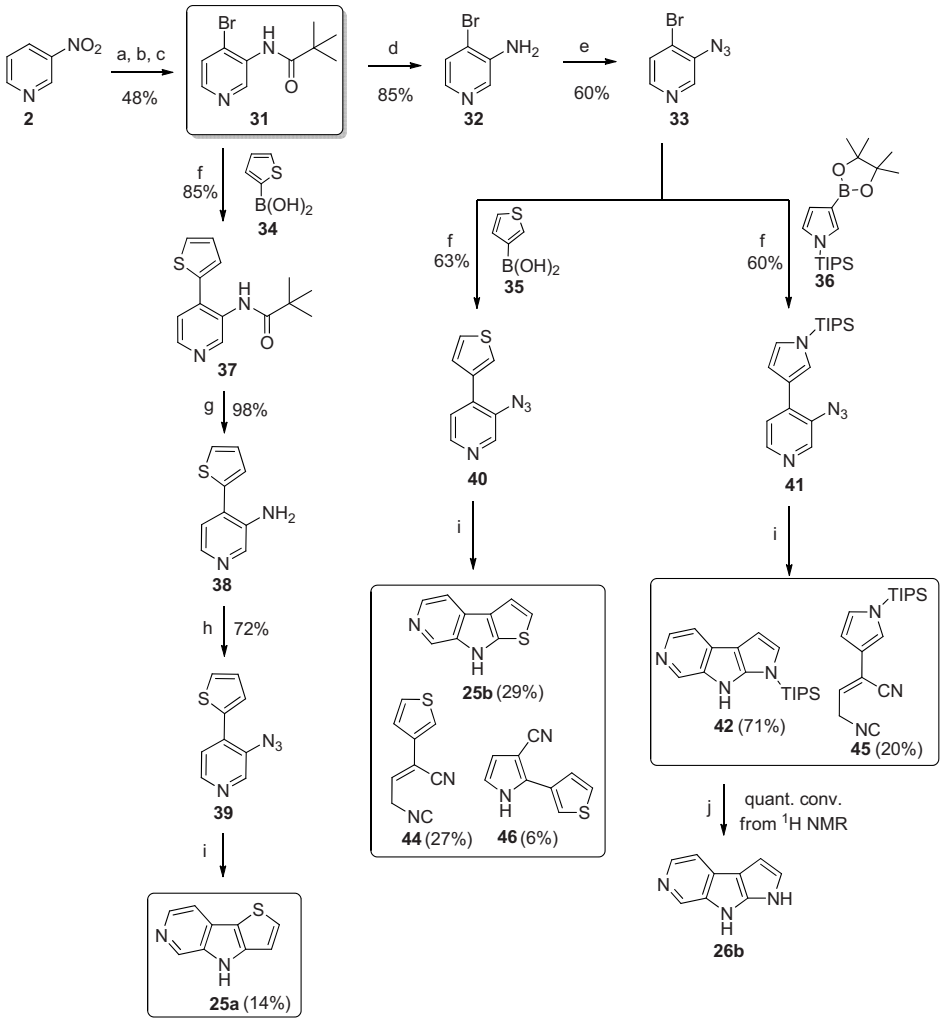
2.2 Results and discussion

The synthetic sequences for the preparation of β-carboline analogues **25a**, **25b** and **26b** and the fused 7-azacinnolines **28a**, **28b**, **29b** and **30b** are presented in Scheme 7 and Scheme 11, respectively. These two new groups of tricyclic heterocycles were prepared from 3-nitropyridine (**2**) through seven- and six-step pathways. The synthetic pathways for all the target products were based on the Suzuki coupling for the preparation of the essential thiophen/pyrrol/furan-ylpyridine intermediates.

2.2.1 Preparation of β-carboline analogues

3-Aminopyridine and 3-(pivaloylamino)pyridine[112] were obtained in high yields by nitro-reduction (91%) of 3-nitropyridine (**2**) followed by derivatization with pivaloyl chloride (96%). 3-(Pivaloylamino)pyridine is known to undergo regioselective electrophilic substitution by o*rtho*-lithiation.[113] By using *t*-BuLi for proton abstraction, and subsequent reaction with the electrophilic ethylene dibromide, 4-bromo-3-(pivaloylamino)pyridine (**31**) was isolated in 55% yield (Scheme 7). Initially, using the *n*-BuLi/TMEDA method for the lithiation,[114] the reaction was complicated by nucleophilic attack by the metalating agent at C4 on the pyridine. Such alkylation of 3-(pivaloylamino)pyridine has been previously reported by Turner.[115]

Scheme 7



Reagents and conditions: (a) Pd/C (10 w/%), H_2/5 atm, MeOH, 2-3 days, 91%; (b) Me_3CCOCl, NEt_3, THF, 0 °C - rt, 2 h, 96%; (c) 1. *t*-BuLi, THF, -78 °C - rt. 2. $BrCH_2CH_2Br$, -78 °C - rt, 55%; (d) H_2SO_4 (20%, aq), reflux, 2 h; (e) 1. $NOBF_4$, MeCN, -10 - 0 °C. 2. NaN_3, H_2O/MeCN, -10 - 0 °C; (f) $Pd(PPh_3)_4$, Na_2CO_3 (2M, aq), MeOH/toluene, 80 - 90 °C; (g) H_2SO_4 (25%, aq), reflux, 3 h; (h) 1. $NaNO_2$ in H_2O, H_2SO_4 (conc). 2. NaN_3 in H_2O, 0 °C; (i) *n*-decane, reflux, 30 - 40 min; (j) NMR-sample: TBAF, $CDCl_3$.

In Suzuki-Miyaura cross-coupling reactions[116] i) electron-deficient aryl halides and ii) electron-rich boronic acids are the substrates of choice, since those compounds are more reactive than the contrary in, respectively, i) the oxidative addition and ii) the

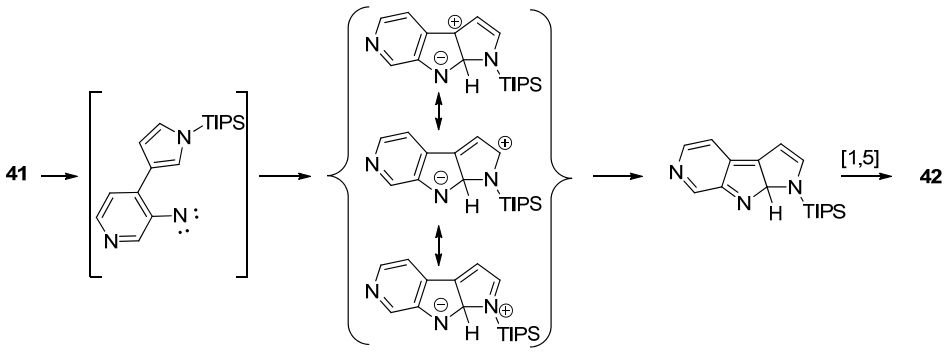
transmetallation steps. The cross-coupling reaction[117] of 4-bromopyridine **31** with commercially available 2-thienylboronic acid (**34**) afforded the corresponding thien-2-ylpyridine coupling product **37** in high yield (85%). Acidic hydrolysis afforded the aminopyridine intermediate **38** in quantitative yields. Diazotization of aminopyridine **38** and subsequent nucleophilic substitution of the diazonium group with azide afforded the azide product **39** in 72% yield. This sequence was not suited for the preparation of azides **40** and **41** as diazotization of the corresponding amines would give the cinnoline products **28b** and **29b** due to the highly reactive 2-positon of the thiophene and pyrrole rings (see part 2.2.3). By exchanging the order of the Suzuki coupling, the hydrolysis and diazotization steps described above, an alternative pathway was used for the preparation of the azide product **40** and **41** (Scheme 7). Hydrolysis of intermediate **31** (85%) followed by $NOBF_4$ diazotization and azide substitution (60%) afforded azide **33** *via* amine **32**. Subsequent Suzuki coupling[117] with commercially available 3-thienylboronic acid (**35**) and the previously described[118,119] 3-pyrrolylboronate reagent **36** afforded the azides **40** and **41**, respectively.

Thermal decomposition of azides **39** and **40** at 174 °C and subsequent CH insertion of the resulting nitrene intermediate gave the desired β-carboline analogues, *4H*-6-azathieno[3,2-*b*]indole (**25a**) and 8*H*-6-azathieno[2,3-*b*]indole (**25b**), respectively. As might be expected from the higher reactivity of the 2-position of the thiophene compared to the 3-position, increased yield was obtained by cyclization of azide **40** to give azaindole **25b** (29%) when compared to azide **39** for the formation of azaindole **25a** (14%). Thermolysis and cyclization of azidopyridine **41** afforded the TIPS-pyrrole carboline analogue **42** (71%). The significantly higher yield obtained for **42** indicates that the highly electron rich *N*-TIPS-pyrrole in substrate **41** offers an activating effect which may compensate for the electron-deficient character of the pyridine ring. Desilylation of azaindole **42** was carried out by TBAF cleavage.[119] Full conversion into the deprotected 1*H*,8*H*-6-azapyrrolo[2,3-*b*]indole (**26b**) was obtained directly, as shown by NMR of the reaction mixture.

The conversion of 2-azidobiphenyl into carbazole (**II**) presumably takes place *via* the formation of a singlet nitrene from the azide which then formally inserts into the CH bond.[120] The formation of carbazole (**II**) reportedly involves concerted cyclization of a singlet nitrene followed by 1,5-hydrogen shift.[121-123] The regiospecific formation of azaindole **42**, in addition to the higher yield obtained when compared to **25a-b**, may be rationalized by a similar mechanism, as outlined in Scheme 8 for the decomposition of azide **41**.

By accepting this model, the preferential electrophilic attack of the nitrene on the 2-position of the TIPS-pyrrole can be rationalized by taking into account that three resonance contributors of the intermediate **43** can be drawn versus two in the case of pyrrole-C3 attack. In addition, the electron density is larger on C2 than on C3. A more electron rich aryl group gives a more stabilized intermediate, something which might explain the higher yield obtained of β-carboline analogue **42** when compared to the thiophene analogues **25a** and **25b**.

Scheme 8



The preparation of *4H*-6-azathieno[3,2-*b*]indole (**25a**) and 8*H*-6-azathieno[2,3-*b*]indole (**25b**) is described in Paper I. The crystal structure of **25b** was solved as a part of this study (Paper IV). The preparation of 1*H*,8*H*-6-azapyrrolo[2,3-*b*]indole (**26b**) is described in Paper II.

2.2.2 Formation of new 4-isocyanobut-2-enenitriles

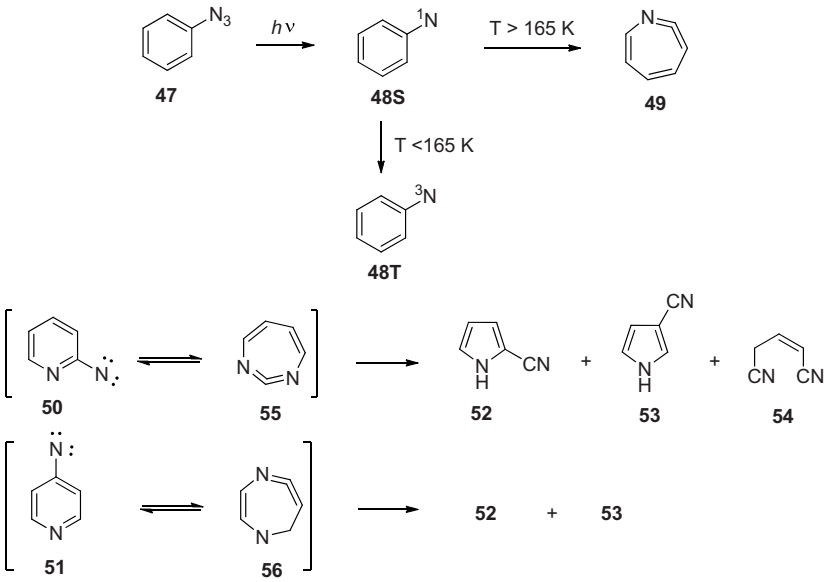
The thermal decomposition of azides **40** and **41** allowed for the isolation of two new, considerably less polar compounds **44** (27%) and **45** (20%). Minor amounts of an additional product **46** (6%) was isolated from the reaction mixture using the thienyl substrate **40** (Scheme 7).

The structure elucidation of the new compounds **44**, **45** and **46** were based on spectroscopic data and chemical characteristics described in Paper III. In general, all NMR, IR and MS data, including results obtained by a thorough 2D NMR correlation experiments (APT, NOESY, HSQC and HMBC) supported the structures reported. However, the most striking feature of compounds **44** and **45** was the triplet splitting of the C4 methylene (-$\underline{C}H_2$-NC) and the isonitrile carbon (-N$\underline{C}$) ^{13}C NMR signals. This

phenomenon is characteristic for alkylisonitriles. Similar spin ^{13}C-^{14}N coupling constants have been reported for analogous -CH_2-NC systems.[124-127] Due to the electronic symmetry of the isonitrile nitrogen nucleus, coupling to the quadrupolar ^{14}N is observable. For this reason the ^{13}C NMR signal for a carbon next to an isonitrile appears as a triplet.

It is well established that photolysis of phenylazide (**47**) releases singlet phenylnitrene (**48S**) which in solution (T > 165 K) rapidly rearranges to 1,2-azacycloheptatetraene **49**.[128,129] At temperatures below 165 K, **48S** preferentially relaxes to triplet phenylnitrene **48T** instead (Scheme 9).[130] The chemistry of 2- and 4-pyridyl nitrenes (**50** and **51**) has previously been investigated.[131] In particular, gas phase pyrolysis studies[132] at temperatures above 480 °C showed the formation of 2- and 3-cyanopyrrole **52** and **53**, as well as minor amounts of the dicyano compound **54**. The stable intermediate in the interconversion of 2- and 4-pyridyl nitrenes has been formulated as the carbodiimide **55** and the ketenimine **56**. In contrast, no studies were carried out on 3-pyridyl nitrenes.

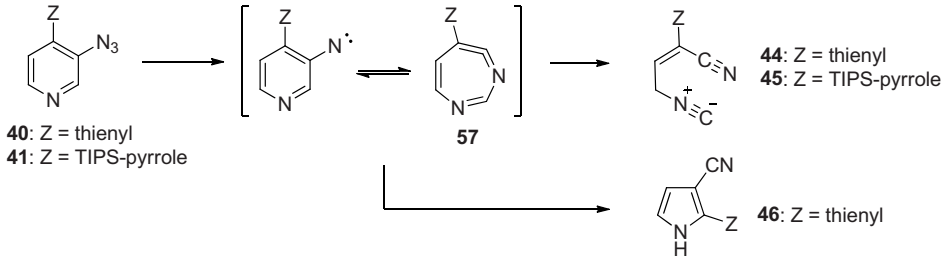
Scheme 9



For the decomposition of azide **40** and **41** we can assume that, in addition to the nitrene CH insertion to form the β-carboline analogues, the nitrene forms a stable

ketenimine intermediate **57**, due to the high temperature (174 °C) used in these experiments (Scheme 10). A ring opening mechanism would explain the formation of the nitrile isonitrile products **44** and **45**. A ring contraction would explain the formation of pyrrole product **46**.

Scheme 10



Isonitriles can rearrange thermally (>270 ^{0}C) into nitriles by pyrolysis.[133,134] Consequently, the previously reported dicyano product **54** (Scheme 9)[132] may have been formed by thermal rearrangement of an initially formed isonitrile-nitrile precursor, due to the harsh pyrolysis conditions employed.

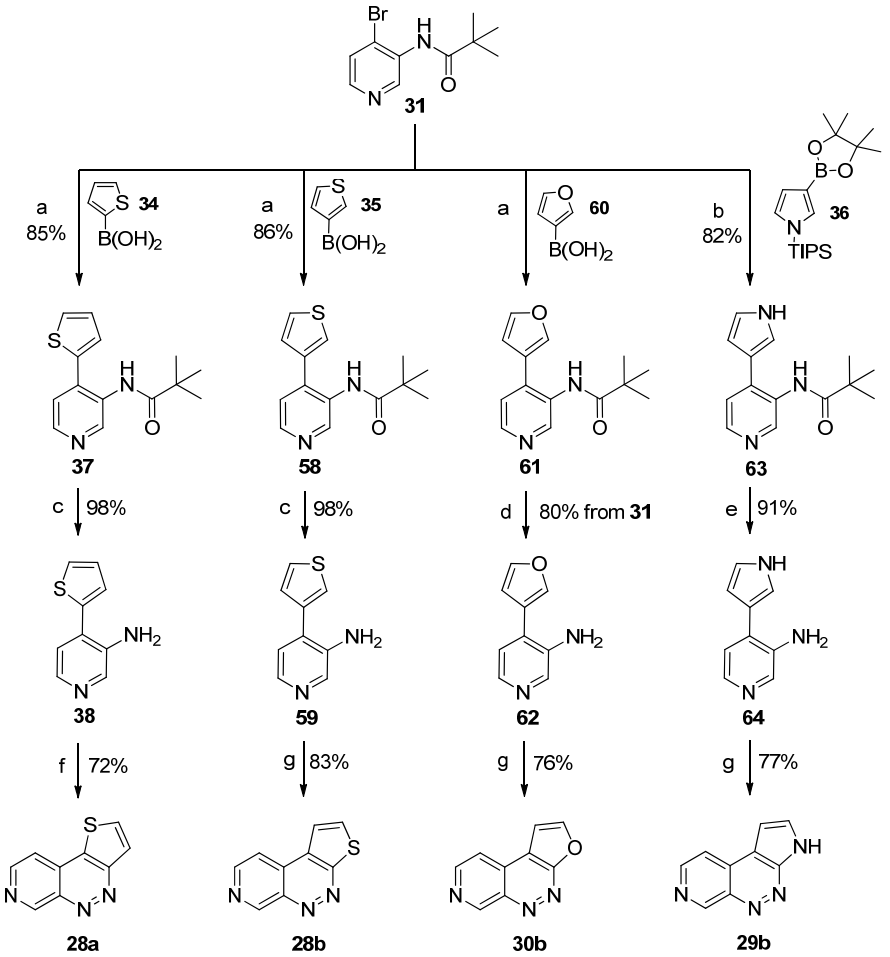
The formation and structure elucidation of 4-isocyanobut-2-enenitriles **44** and **45** and 2-(thiophen-3-yl)-1*H*-pyrrole-3-carbonitrile (**46**) are fully described in Paper III.

2.2.3 Preparation of fused 7-azacinnolines

The synthetic pathway for the fused 7-azacinnolines **28a**, **28b**, **29b** and **29b** was based on the Suzuki coupling for the preparation of the essential thiophen/furan/pyrrol-ylpyridine intermediates, as shown in Scheme 11. The diaryl-coupling products **37**, **58** and **61** were prepared by coupling of 4-bromopyridine **31** and the commercially available thiophen/furan-ylboronic acids **34**, **35** and **60**. In the coupling reaction of bromide **31** and the *N*-TIPS-pinacolatopyrroloboronate ester **36**,[118] using $K_3PO_4 \cdot 3H_2O$ and the Pd_2dba_3-SPhos catalytic system,[135] the *N*-TIPS group was cleaved to give the deprotected pyrrol product **63**. An additional desilylation step was, therefore, not required. Acidic hydrolysis of amides **37** and **58** afforded the aminopyridine intermediates **38** and **59** in quantitative yields. It is well known that protonation of pyrroles and furans takes place in acidic media and often leads to hydrolysis, cleavage or rapid polymerisation / oligomerisation of the cations.[136] Thus, alkaline hydrolysis was selected for the conversion of pivalamides **61** and **63** to afford the unprotected aminopyridines **62** (80% from **31**) and **64** (91%).

The amines **38**, **59**, **62** and **64** represent appropriate intermediates for the formation of intramolecular diazo coupling products as an electron-rich heteroaromatic ring and an electron-deficient pyridine moiety are both present.

Scheme 11



Conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3 (2M, aq), MeOH/toluene, 80 - 90 °C, overnight; (b) Pd_2dba_3, SPhos, $K_3PO_4 \cdot 3H_2O$, *n*-butanol/H_2O, 100 °C, overnight; (c) H_2SO_4 (25%, aq), reflux, 3h; (d) NaOH (8 M, aq), EtOH (96%), reflux, 70 h; (e) NaOH (8 M, aq), EtOH (96%), reflux, 26 h; (f) $NaNO_2$ in H_2O, H_2SO_4 (conc), 0 °C - rt, overnight; (g) $NOBF_4$, MeCN, 0 °C, 45 min.

The higher reactivity of the 2-position compared to the 3-position of the thiophene was demonstrated by the fact that strongly acidic conditions ($NaNO_2/H_2SO_4$, see Scheme 11) was definitely required for the successful conversion of thien-2-yl **38** to 7-azathieno[3,2-*c*]cinnoline (**28a**). The strong acid activates the diazonium group by protonation of the pyridine moiety. No such activation was needed for diazo coupling of the thien-3-yl **59** to give 7-azathieno[2,3-*c*]cinnoline (**28b**), as this reaction took place using $NOBF_4$/MeCN (83%). By using $NaNO_2/H_2SO_4$, **28b** was formed in a slightly lower yield (73%). Due to the electron-deficient and hence more reactive thienopyridine diazonium ion, the obtained yields of the present azacinnolines **28a** and **28b** were considerably higher than those reported for the corresponding thienophenyl diazonium analogues for the formation of thieno[3,2- and 2,3-*c*]cinnolines (13% and 69%).[137]

Traditional acidic conditions ($NaNO_2/H_2SO_4$) also had to be avoided for the diazotization of amines **62** and **64**. Exclusive formation of 7-azafuro[2,3-*c*]cinnoline (**30b**, 76%) and 3*H*-7-azapyrrolo[2,3-*c*]cinnoline (**29b**, 77%) were obtained by intramolecular diazo coupling of the diazonium intermediate generated by $NOBF_4$ from aminopyridines **62** and **64**, respectively.

To the best of our knowledge, this is the first reported intramolecular diazo coupling of furans. Furan has considerably less aromatic stabilization than pyrrole and react, in general, with electrophiles to give addition products rather than substitution products.[138] While diazo coupling occurs readily between pyrroles and benzenediazonium salts, furan undergoes phenylation rather than diazo coupling on reaction with benzenediazonium salts.[139] On the other hand, 2,5-dimethylfuran can give normal coupled products with 2,4-dinitrobenzenediazonium ion, but the outcome of the reaction is very dependent on the reaction conditions.[140]

The preparation of 7-azathieno[3,2-*c*]cinnoline (**28a**) and 7-azathieno[2,3-*c*]cinnoline (**28b**) is described in Paper I. The crystal structure of azacinnoline **28a** (Paper V) and azacinnoline **28b** (VI) was solved as a part of this study. The preparation of 3*H*-7-azapyrrolo[2,3-*c*]cinnoline (**29b**) and 7-azafuro[2,3-*c*]cinnoline (**30b**) is described in Paper II.

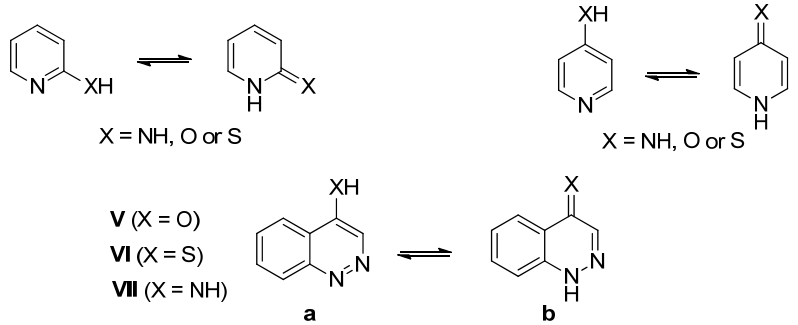
3 Preparation of 7-azacinnolin-4(1*H*)-one

This chapter summarizes results presented in paper VII. Sebastian Primpke worked on this project as a part of an Erasmus exchange program and is acknowledged for his contribution. PhD Trygve Andreassen is acknowledged for technical assistance during the ^{15}N NMR experiments.

3.1 Background

Prototropic tautomerism in heterocyclic chemistry has attracted large research efforts over the years, and has been reviewed by Katritzky with others.[141-147] Heteroaromatic tautomerism is of highly biological importance as DNA, the carrier of all genetic information, consists of two intertwining helices held together by the so-called base pairing. The tautomeric form of the nucleic acid bases is crucial to this base pairing. Tautomerism is defined as a phenomenon in which two or more molecular structures exist in dynamic equilibrium with each other, i.e. the energy barrier between them is small. Considering prototropic tautomerism, where a proton moves from one position in a molecule to another, the phenomenon is illustrated in Scheme 12. Experimental and theoretical methods have shown that aminopyridines exist largely as amino tautomers, while α- and γ-pyridones and α- and γ-thiopyridones exist largely in the oxo or thioxo forms in aqueous solution.[142,143] Similarily, cinnolin-4-ol (**Va**) and cinnoline-4-thiol (**VIa**) predominantly exist as oxo **Vb** or thioxo **VIb** tautomers, whereas the amino form **VIIa** is preferred for cinnolin-4-amine (**VIIa**).[148]

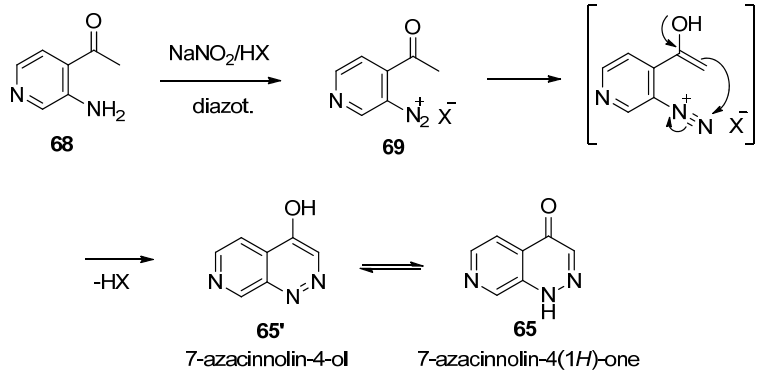
Scheme 12



Recent NMR spectroscopic investigations of cinnolines **V**, **VI** and **VII** have revealed that these compounds exist exclusively in the oxo form **Vb**, thioxo form **VIb** and amino form **VIIa** in DMSO-d_6.[149] Cinnolin-4(1*H*)-one (**Vb**), often referred to as cinnolin-4-ol (**Va**), is

prepared from 2-aminoacetophenones by the Borsche synthesis,[150-152] by cyclocondensation of the corresponding diazonium salts in aqueous solution. Applying the same strategy, a novel pyridine analogue **65** would be synthesized from 4-acetyl-3-aminopyridine (**68**) by cyclization of diazonium intermediate **69**. It is assumed that the cyclization takes place through the formation of the enolic form of the ketone (Scheme 13).[87]

Scheme 13



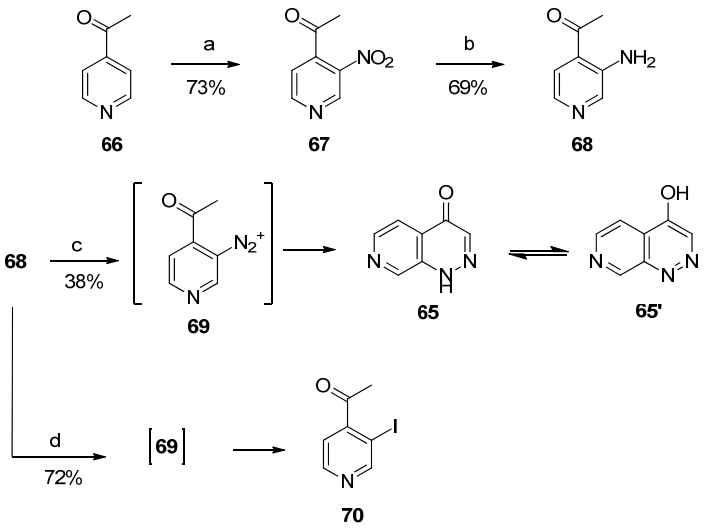
A previous investigation reported unsuccessful ring-closure of 4-acetyl-3-aminopyridine (**68**) after diazotization.[153] Applying either acidic or alkaline conditions, no products arising from cyclization were observed. The synthesis of the aminopyridylketone **68** was also reported to be extremely difficult and was eventually achieved by ozonolysis of the corresponding benzamidopyridylpropene and subsequent hydrolysis.

3.2 Results and discussion

Our three-step synthesis for the preparation of 7-azacinnolin-4(1*H*)-one (**65**) from 4-acetylpyridine (**66**) is shown in Scheme 14. Pyridine **66** was nitrated to give 4-acetyl-3-nitropyridine (**67**). By minor modifications of the nitration method using N_2O_5 in an organic solvent and $NaHSO_3$ in MeOH-H_2O (3:1),[31] we were able to increase the yield of **67** from 58% to 73%. The nitropyridine **67** was reduced with $Na_2S_2O_4$ in EtOH to prevent reduction of the ketone,[154] and amine **68** was obtained in 69% yield, as previously reported.[42] Based on the Borsche synthesis, we developed a procedure for the formation of 7-azacinnoline-4(1*H*)-one (**65**). The diazo coupling product **65** was obtained in 38% yield by diazotization with $NaNO_2$/HCl (aq) in EtOH and subsequent cyclization in alkaline medium by slow addition of NaOH in EtOH/H_2O.

A recent report has described iodination of aryl amines in a water-paste form *via* stable aryl diazonium tosylates.[155] We were able to prepare the previously unknown 4-acetyl-3-iodopyridine (**70**) in high yield (72%) when we tested this diazotization method on aminopyridine **68**. Unfortunatly, we were not able to identify conditions that successfully enabled cyclization of the aryl diazonium tosylat **69**. The highest yield (20%) of azacinnolinone **65** was obtained by using a phosphate buffer at 0 °C for the cyclization of aryl diazonium tosylate **69**.

Scheme 14



Reagents and conditions: (a) 1. N_2O_5 in $MeNO_2$, 0 °C, 2. $NaHSO_3$ in $MeOH/H_2O$; (b) $Na_2S_2O_4$ in EtOH, reflux, 6 h; (c) 1. $NaNO_2$ in HCl/H_2O/EtOH, 0 °C, 2. NaOH in H_2O/EtOH, -10 °C; (d) 1. $NaNO_2$ in *p*-TsOH/H_2O, 2. KI

Detailed NMR spectroscopic investigations (Figure 3) revealed that azacinnolinone **65** exists exclusively in the NH-keto tautomeric form in DMSO-d_6. The δ_N-values were obtained from ^1H-^{15}N HMBC experiments, and are reported downfield from liquid ammonia. The observed chemical shift values for azacinnolinone **65** were in accordance with the reported ^1H, ^{13}C and ^{15}N NMR chemical shifts for cinnolin-4(1*H*)-one (**Vb**).[149] NOESY experiments demonstrated that the acidic proton at 13.93 ppm represented the =N-NH

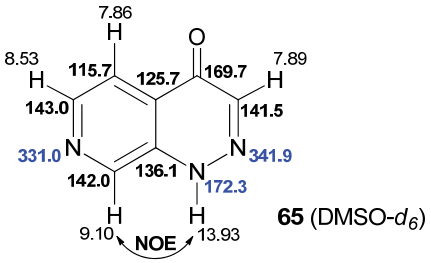


Figure 3. ^{1}H-, ^{13}C- and ^{15}N-NMR chemical shifts of 7-azacinnolin-4(1*H*)-one (**65**).

$CDCl_3$ was not suitable as solvent, as 7-azacinnolinone **65** was nearly insoluble in non-polar solvents. Similar ^{1}H and ^{13}C NMR chemical shift values were observed for azacinnolinone **65** in polar protic solvents, such as D_2O and CD_3OD, as in DMSO-d_6. The presence of the carbonyl signal for C4 in CD_3OD (174.0 ppm) and in D_2O (174.6 ppm), confirmed that the keto tautomeric form **65** exclusively dominates in these solvents as well.

To summarize, 7-azacinnolin-4(1*H*)-one (**65**) has successfully been prepared by an intramolecular C-azo coupling from 4-acetyl-3-aminopyridine (**68**) *via* diazotization. Detailed NMR spectroscopic investigations (^{1}H, ^{13}C, ^{15}N) revealed that the azacinnoline exists exclusively in the NH-keto tautomeric form **65** in DMSO-d_6, CD_3OD and D_2O.

4 Synthesis of novel 1,7-naphthyridines

This chapter summarizes results presented in paper VIII.

4.1 Background

Naphthyridines (pyridopyridines, diazanaphtalenes) are heterocyclic system containing two fused pyridine rings. The six possible isomeric structures are shown in figure 4.

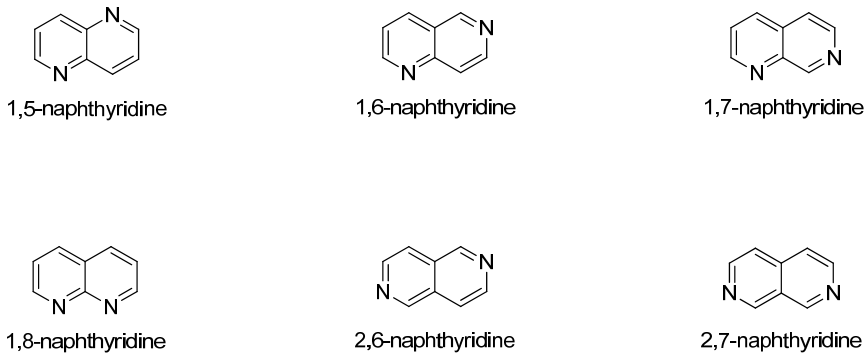


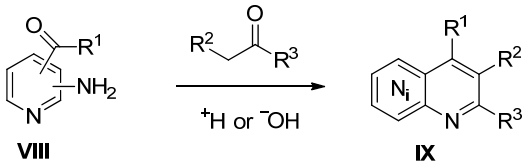
Figure 4. Naphthyridines

Naphthyridine derivatives attract interest because of their broad spectrum of biological activities and practical importance. Their synthesis, properties, reactivity and biological activity have been covered in several reviews by Litvinov.[156-159] These compounds are used in diagnostics and treatment of different bacterial and viral (HIV) infections, and are synthesized as potential antimalarials and anticancer agents. They are also used in agriculture, for parasite control, as preservatives and components of lubricating coolants in industry, for metal processing and in analytical chemistry as ligands. The biological activities of 1,8-naphthyridine derivatives have received most attention.[156] However, 1,7-naphthyridines have recently attracted interest as selective Tumor Progression Loci-2 (Tpl2) kinase inhibitors as the kinase is an attractive target for the treatment of rheumatoid arthritis.[160-162] In addition, 1,7-naphthyridines have shown antiparasitic activities,[163] and potential as new therapeutic antitumor agents.[164]

A general procedure for the preparation of naphthyridines **IX** is the base- or acid-promoted condensation of vicinal aminopyridinecarbonyl compounds **VIII** with an

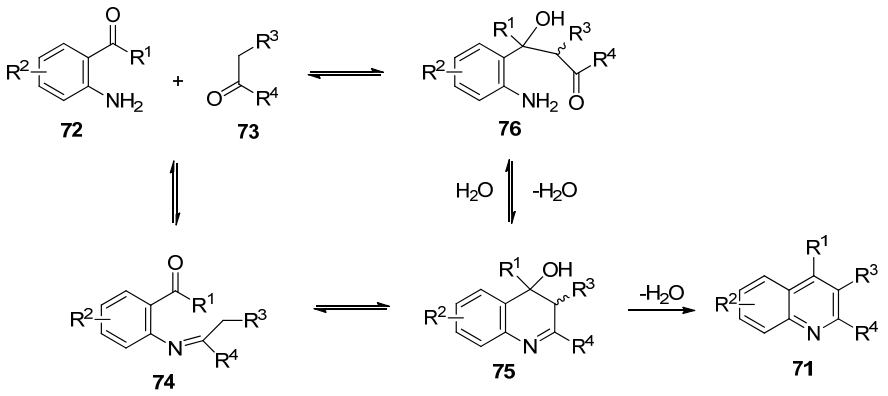
appropriately substituted carbonyl derivative containing a reactive α-methylene group, known as the Friedländer reaction (Scheme 15).[156,165]

Scheme 15



Originally, this reaction was used for quinoline syntheses from *o*-aminobenzaldehyde, and is today one of the most important tools for preparation of quinoline derivatives.[165-167] The mechanism of the Friedländer reaction has not been unambiguously established,[168] and the two possible pathways for the formation of quinoline **71** from 2-amino aryl carbonyl compound **72** and carbonyl compound **73** are outlined in Scheme 16.[165]

Scheme 16



Most studies have favored a mechanistic pathway involving the initial formation of the Schiff base **74** followed by an intramolecular aldol reaction to give the hydroxy imine **75**. Elimination of water affords the quinoline **71**.[169-171] However, mechanistic support for an initial intermolecular aldol reaction to afford intermediate **76** exists.[172] Finally, a

recent study has concluded that under typically acidic (HCl, H_2SO_4) or basic (NaOH) conditions, a slow intermolecular aldol reaction is the first step.[173]

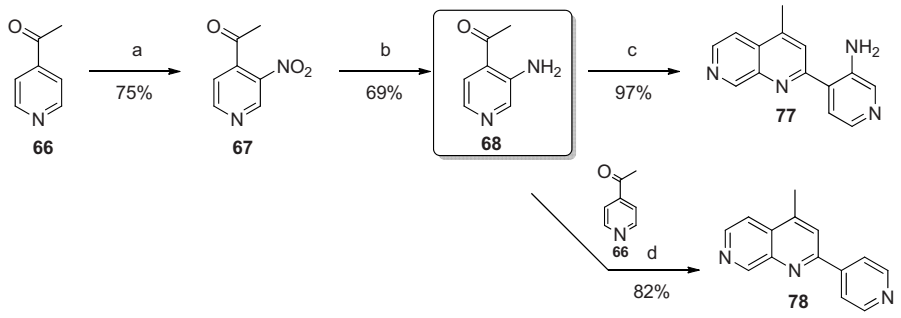
While the Friedländer reaction has been widely used for preparation of 1,8-naphthyridines from 2-amino-3-pyridinecarboxaldehyde,[174-181] its use in the preparation of 1,7-naphthyridines[179,182-184] has been limited. Apparently, the complicated preparation of the starting 3-aminopyridine-4-carbonyl compounds, such as 3-amino-4-pyridinecarboxaldehyde (**83**),[115,182] has been a contributing factor.

As we had convenient access to simple aminopyridinecarbonyl compounds, such as 3-amino-4-acetylpyridine (**68**) and 3-amino-4-pyridinecarboxaldehyde (**83**) from nitropyridines, we wanted to investigate the synthesis of 1,7-naphthyridines by the Friedländer reaction.

4.2 Results and discussion

4-Acetyl-3-aminopyridine (**68**) was obtained as previously described in Chapter 3.2. Aminopyridylketone **68** reacted in a Friedländer self-condensation by treatment of excess NaH in dry THF to afford the 1,7-naphthyridine **77** in quantitative yield (Scheme 17). To expand the scope of the reaction, we showed that the dimerization to product **77** could be suppressed when aminopyridylketone **68** was reacted with another ketone **66**. Optimized reaction conditions gave naphthyridine **78** in 82% yield and small amounts of naphthyridine **77** (10%) as a byproduct.

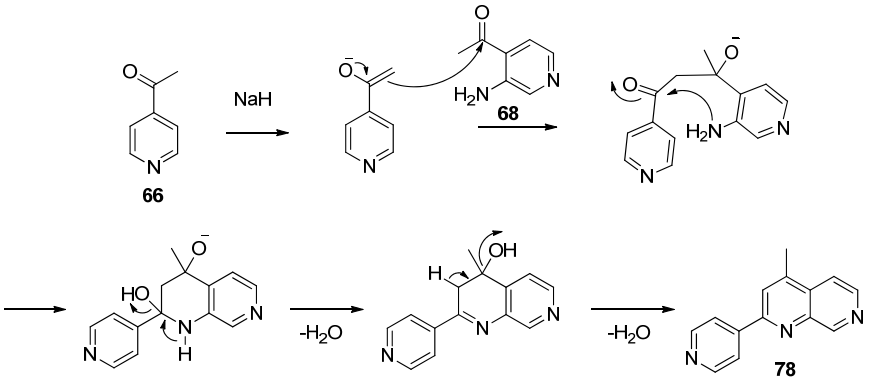
Scheme 17



Reagents and conditions: (a) 1. N_2O_5 in $MeNO_2$, 0 °C, 2. $NaHSO_3$ in $MeOH/H_2O$; (b) $Na_2S_2O_4$ in EtOH, reflux, 6h; (c) NaH, THF, 0 °C - rt, 2h; (d) NaH, THF, rt, 2h

Some important experimental observations were noted during the optimization of the reaction conditions for the preparation of naphthyridine **78**, in order to avoid the self-condensation product **77**. As expected, an excess of ketone **66** (1.2 eq) needed to be treated with NaH (1.1) before the addition of aminopyridylketone **68**. In addition, the yield of product **78** was increased twofold by rising the temperature from 0 °C to room temperature, thus allowing full deprotonation of ketone **66** before addition of substrate **68**. The latter observation indicates that under these conditions the Friedländer reaction proceeds through an initial intermolecular aldol reaction as illustrated in Scheme 18.

Scheme 18

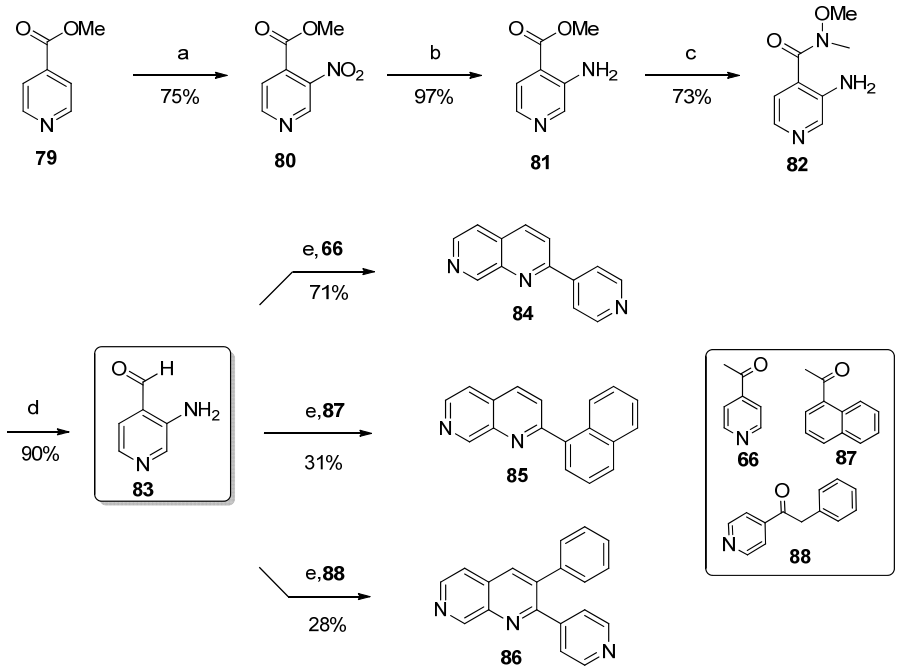


To further expand the scope of the reaction, 3-aminoisonicotinaldehyde (**83**) was tested as a substrate to demonstrate the general potential of pyridyl substrates for the preparation of 1,7-naphthyridines by the Friedländer condensation (Scheme 19). Methyl 3-aminoisonicotinate (**81**) was obtained after nitration of methyl isonicotinate (**79**) and subsequent reduction of nitropyridine **80**.[42] By using the Me_2AlCl/MeONHMe·HCl reagent system,[185] aminoisonicotinate **81** was transformed into the corresponding Weinreb's amide **82** (73%). Following reduction with $LiAlH_4$, 3-aminoisonicotinaldehyde (**83**, 90%) was obtained.

Friedländer reactions of 3-amino-4-pyridinecarboxaldehyde (**83**) with the respective ketones **66**, **87** and **88**, using 2-2.5 equiv NaH in THF, gave the 2-aryl and 2,3-diaryl-1,7-naphthyridines **84**-**86**. While ketones **66** and **87** were commercial available, ketone **88** was prepared from isonicotinaldehyde *via* 4-dimethoxymethylpyridine, BuLi proton abstraction, subsequent nucleophilic substitution of benzylchloride and hydrolysis.[186] Naphthyridine **84** has previously been prepared by standard Friedländer conditions

(NaOH/EtOH) in lower yield[184] (60%) than obtained by our alternative NaH/THF method (71%). The novel products **85** and **86** were obtained in 28 - 31% yield due to the formation of unidentified by-products. The yields of products **84**-**86** were not influenced by the order of reactant addition.

Scheme 19



Reagents and conditions: (a) 1. N_2O_5 in $MeNO_2$, 0 °C, 2. $NaHSO_3$ in $MeOH/H_2O$; (b) $Na_2S_2O_4$ in EtOH, reflux, 6h; (c) MeONHMe·HCl/Me_2AlCl (1 M in hexanes), DCM, rt, 20 h; (d) $LiAlH_4$ in THF, -15 °C; (e) NaH in THF, 0 °C - rt, 2 h.

To summarize, the pyridine nitration pathway followed by Friedländer condensation represent a convenient strategy for the preparation of 1,7-naphthyridines. Optimized reaction conditions allowed 4-Acetyl-3-aminopyridine (**68**) and 4-acetylpyridine (**66**) to react in a Friedländer reaction to afford 2,4-disubstituted 1,7-naphthyridine **78** (82%). By treatment of pyridine **68** with an excess of NaH, the self-condensation product, 1,7-naphthyridine **77**, was obtained in quantitative yield. 3-Aminoisonicotinaldehyde (**83**) reacted by Friedländer condensation with arylketones **66**, **87** and **88** to give 2-aryl and 2,3-diaryl-1,7-naphthyridines **84**-**86** (28-71%).

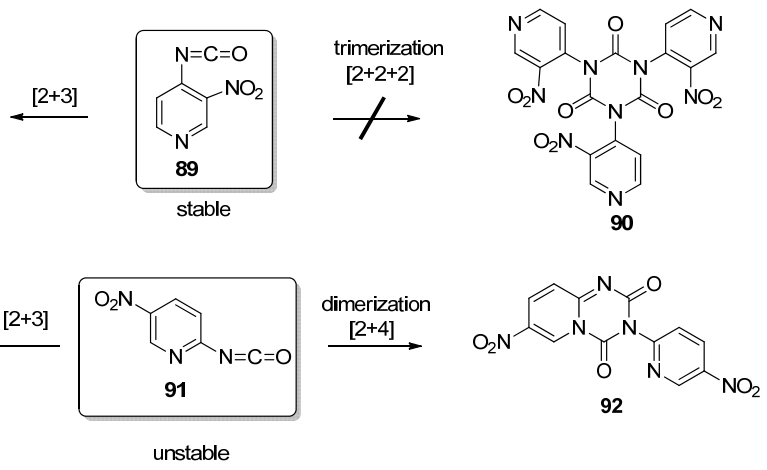
5 Cycloaddition reactions with pyridyl isocyanate and 3,4-pyridyne

Kai Felix Kalz worked on this project as a part of an Erasmus exchange program and is acknowledged for his contribution.

5.1 Background

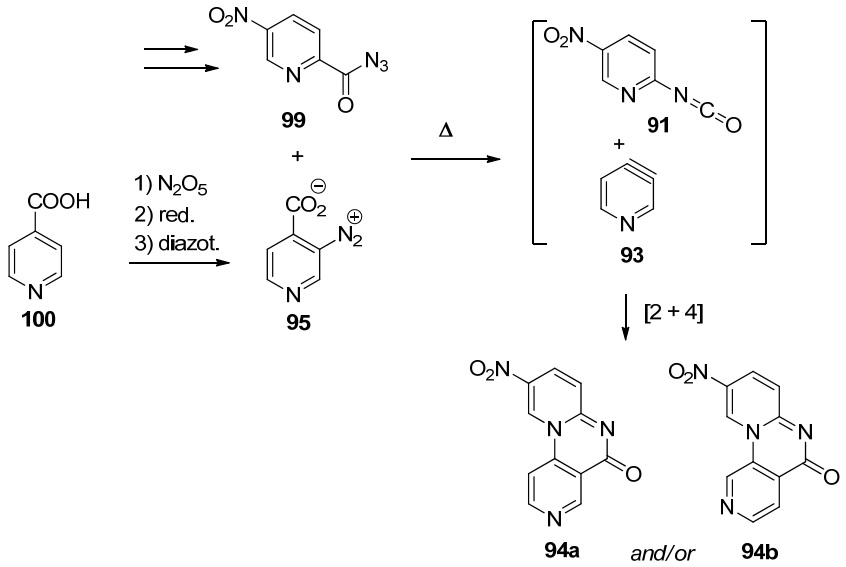
Heteroaromatic isocyanates have not been given the same attention as other aromatic isocyanates. 2-Pyridyl isocyanate and 4-pyridyl isocyanate have not been isolated and characterised, due to their instability and high reactivity,[187] and have been reported to undergo spontaneous di- or trimerisation.[188] The research group of Fiksdahl reported in 2005 the synthesis and characterisation of nitropyridyl isocyanates **89** and **91**.[46] The introduction of an electronegative nitro-substituent reduced the basicity of the pyridine nitrogen and hence the susceptibility for di- or trimerisation. 3-Nitro-4-pyridyl isocyanate (**89**) could be stored in dry diethyl ether or benzene solutions and was stable at room temperature for several weeks. However 5-nitro-2-pyridyl isocyanate (**91**) was less stable and had to be used for synthetic purposes immediately to avoid dimer formation by [2+4] cycloaddition to give adduct **92** (Scheme 20).

Scheme 20



In 2007, the Fiksdahl group demonstrated the synthetic application of nitropyridyl isocyanats **89** and **91** in 1,3-dipolar cycloaddition reactions, and isolated a series of new [2+3] cycloaddition products.[47] Based on this project, we wanted to investigate the [2+4] cycloaddition reaction between nitropyridyl isocyanate **91** and 3,4-pyridyne (**93**), as shown in Scheme 21. Both reactants can be prepared *in situ* from their respective precursors. The acyl azide **99** undergoes Curtius rearrangement to give isocyanate **91**, and the diazonium carboxylate **95** would decompose into pyridyne **93**, by heating. The expected cycloadducts in the Diels-Alder reaction would be the regioisomeric pyridopyrimidinones **94a** and/or **94b**. Diazonium carboxylate **95** would be available from isonicotinic acid (**100**) by nitration, reduction and diazotization.

Scheme 21



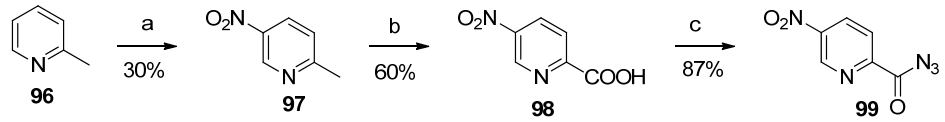
Previous reports have suggested that 3,4-pyridyne (**93**) has less predictable dienophilic (and dipolarophilic) character than benzyne.[189,190] Theoretical calculations on pyridyne **93** have shown the electron density of the LUMO of **93** to be evenly distributed on C3 and C4.[191] Accordingly, the two orientations are almost equally likely for cycloaddition.[192,193] However regiospecific formation of adducts in 1,3-dipolar reactions of hetarynes has been reported,[194] and a mechanism involving a zwitterionic hetaryne precursor has been suggested. A regioselective formation of products **94a** or **94b** would provide further insight into the mechanism involving pyridyne precursors.

5.2 Results and discussion

In order to investigate the [2+4] cycloaddition reaction between isocyanate **91** and pyridyne **93**, their respective precursors **99** and **103** were prepared.

The isocyanate precursor, 5-nitropicolinoyl azide (**99**), was prepared as previously described (Scheme 22).[31,46,195] By nitration of 2-picoline (**96**) and subsequent oxidation of nitropicoline **97**, 5-nitropicolinic acid (**98**) was afforded. The carboxylic acid **98** was transformed directly with diphenyl phosphoryl azide (DPPA) to acyl azide **99** in high yield.

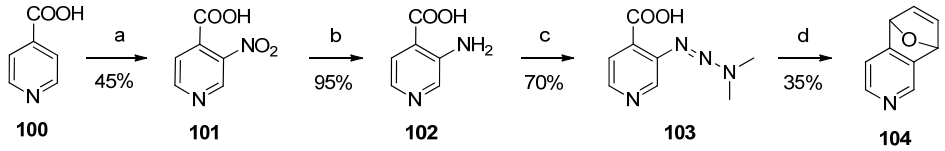
Scheme 22



Reagents and conditions: (a) 1. N_2O_5 in $MeNO_2$, 0 °C, 2. $NaHSO_3$ in $MeOH/H_2O$; (b) CrO_3, H_2SO_4, 70 °C - rt, 20; (c) DPPA, Et_3N, DMF, 35 °C, 2 h.

The precursor of pyridyne **93**, 3-(3,3-dimethyl-triazen-1-yl)isonicotinic acid (**103**) may be regarded as a masked version of pyridine-3-diazonium-4-carboxylate (**95**), and has the advantages of being stable, easy to handle and safe.[196] Triazene **103** was prepared as outlined in Scheme 23. 3-Aminoisonicotinic acid (**102**), readily accessible from isonicotinic acid (**100**) by nitration and reduction,[31,42] was transformed into the triazene **103** by diazotization and subsequent coupling with dimethylamine.[190,196]

Scheme 23

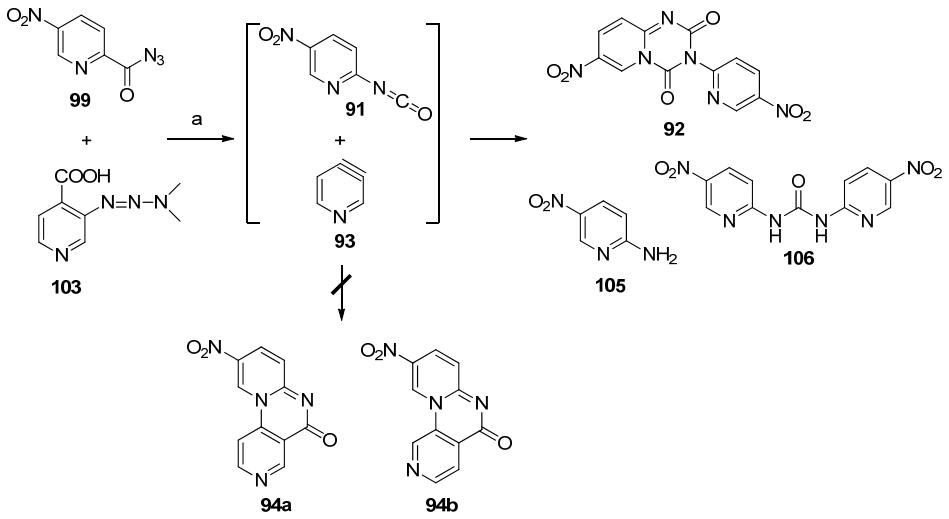


Reagents and conditions: (a) 1. N_2O_5 in $MeNO_2$, 0 °C, 2. $NaHSO_3$ in $MeOH/H_2O$; (b) Pd/C (5 $^{w}/_{\%}$), H_2 (5 atm), MeOH, 2 days; (c) 1. $NaNO_2$, HCl, $EtOH/H_2O$, 2. Na_2CO_3, $HNMe_2$, 0 °C; (d) furan, MeCN, sealed vessel at 130 °C, 4h.

The pyridyl triazene **103** was decomposed into pyridyne **93** and trapped by furan in a [2+4] cycloaddition reaction.[196] The Diels Alder adduct **104** was isolated in 35% yield, and, consequently, the generation of 3,4-pyridyne (**93**) was confirmed.

The preparation of cycloadducts **94a** and **94b** was attempted by heating acyl azide **99** and triazene **103** in different solvents, such as toluene, benzene and MeCN. The crude reaction mixture was analysed by ^{1}H NMR spectroscopy. In all reactions, only products originating from isocyanate **91** were observed, together with unidentified byproducts. The observed dimer **92** is a result of a [2 + 4] cycloaddition reaction of two isocyanate **91** molecules.[46] Amine **105** and urea **106** are formed from isocyante **91** due to the presence of water (Scheme 24).

Scheme 24

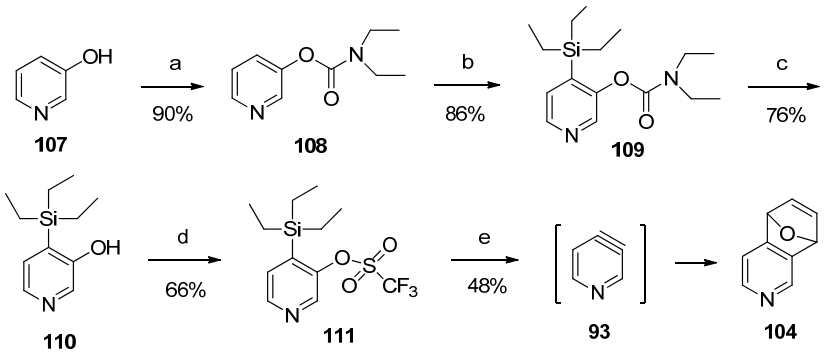


Reagents and conditions: (a) Toluene, reflux, overnight

Even though careful precautions were taken to avoid water in these reactions, amine **105** and urea **106** were observed in variable, but considerable amounts. These products would also be formed through the quenching of the reaction and work-up if isocyanate **91** remained unreacted. Although a more thorough purification of the reaction mixtures in order to establish the ratio between the byproducts **92**, **105** and **106** would be favorable, we realized that the acidic precursor **103** most likely was an unfavorable choice. Therefore, we decided to search for a more suited pyridyne precursor.

We found that successful [2+4] cyclization with pyridyne triflate precursor **111** had been reported.[197,198] 4-Triethylsilylpyridine-3-yl trifluoromethanesulfonate (**111**) was prepared as described by Carroll and co-workers,[198] and similarly high yields were obtained in every step of the reaction sequence (Scheme 25). Pyridin-3-yl diethylcarbamate (**108**) was obtained by derivatization of 3-pyridinol (**107**) with diethylcarbamoyl chloride, in this manner introducing the powerful carbamate *o*-directed metalation group. The 3-pyridyl carbamate **108** was sequentially lithiated with LDA and quenched with TESCl to furnish the 4-silylated product **109** regiospecifically. Even though silylpyridines are sensitive towards base-induced cleavage,[199] carbamate hydrolysis of **109** under basic conditions gave the TES-pyridinol **110** in high yield. This was converted into the triflate **111** by reaction with trifluoromethanesulfonic anhydride in pyridine.

Scheme 25

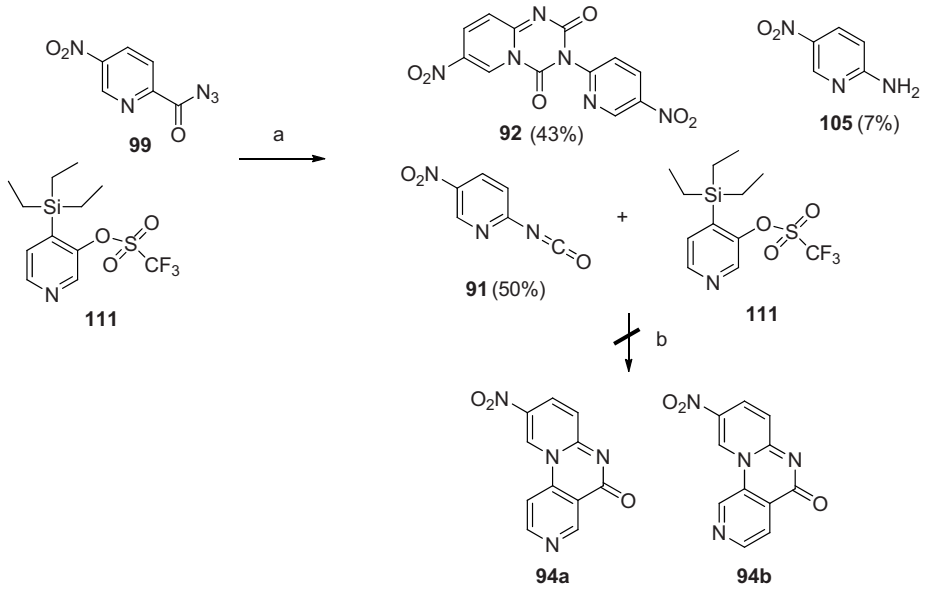


Reagents and conditions: (a) $ClCON(CH_2CH_3)_2$, pyridine, 0 °C - rt, 20 h; (b) 1. LDA (2.0 M), -78 °C, THF, 2. TESCl (1.0 M), -78 °C - rt, 20 h; (c) 20% NaOMe in MeOH, 24 h; (d) $(CF_3SO_2)_2O$, pyridine, 0 °C - rt, overnight; (e) furan, CsF, MeCN/Benzene (1:1), 0 °C - rt, overnight.

The decomposition of the precursor **111** to pyridyne **93** by CsF was tested by trapping with furan in a Diels-Alder reaction to give the cycloaddition product **104**.[200] The reaction was conducted in a mixture of MeCN and benzene to verify that the presence of benzene did not affect the generation of pyridyne **93** from the precursor **111**. This was an important result as the formation of isocyanate **91** by Curtis rearrangement of azyl acide **99** is preferentially carried out in benzene to allow for azeotropic removal of water.

The preparation of cycloadducts **94a** and **94b** was attempted with the new pyridyne precursor **111** as outlined in Scheme 26.

Scheme 26



Reagents and conditions: (a) benzene-d_6, reflux, 15 min, cooled to rt, the reaction mixture was analysed by ^{1}H NMR; (b) CsF, MeCN-d_3, 0 °C - rt, 2h.

The triflate **111** and acylazide **99** was dissolved in benzene-d_6 and moisture was removed by azeotropic distillation under reduced pressure to avoid the formation of amine **105**. The reaction mixture was heated in order to form the isocyanate **91**. Typically, isocyanate **91** was formed as the main product, but the formation of dimer **92** (43%) and amine **105** (7%) could unfortunately not be avoided as shown by ^{1}H NMR. The pyridyne precursor **111** was not affected by the heating, and the reaction mixture was cooled before a solution of CsF in MeCN-d_3 was added to generate pyridyne **93**. Neither product **94a** nor **94b** were observed by NMR spectroscopy of the crude reaction mixture. The crude product mainly consisted of tarry, polar materials and no products were isolated.

To summarize, the main challenges connected to these reactions and which probably are related to why we eventually were unsuccessful in preparing the desired products **94a** and/or **94b** are: 1) the fast dimerization of isocyanate **91** in absence of a suitable

trapping agent, and the relatively slow decomposition of the pyridyne precursors **103** and **111**; 2) the presence of residual water in the reaction mixture, especially when operating on a small scale; 3) while the formation of isocyanate **91** requires low concentration to avoid dimerization, the reaction between pyridyne **93** and isocyanate **93** probably necessitates high concentration of the reactants due to the short lifetime of pyridyne **93**; 4) identifying the right solvent combination as the decomposition of acyl azide **99** is favored in apolar solvents while the decomposition of the pyridyne precursor **103** and **111** is favored in polar solvents.

5.3 Experimental

General. Solvents: *pro analysi* quality. *Dry* toluene was collected from a MB SPS-800 solvent purification system and stored over 4 Å molecular sieves under argon. All reactions were performed under argon atmosphere in pre-dried glassware. NMR: Bruker Avance DPX 400 and 300 MHz spectrometers. ^{1}H chemical shifts are reported in ppm downfield from TMS. *J* values are given in Hz.

Typical cycloaddition attempt from 5-nitropicolinoyl azide (99) and 3-(3,3-dimethyltriazen-1-yl)isonicotinic acid (103). A solution of acylazide **99** (99 mg, 0.52 mmol) in *dry* toluene (5 mL) was heated to 90 °C under an argon atmosphere and stirred for 15 min. A solution of triazene **103** (50 mg, 0.26 mmol) in *dry* toluene (5 mL) was added dropwise and the reaction mixture was kept stirring at 90 °C overnight. The solution was concentrated under reduced pressure to give a brown solid containing isocyanate dimer **92**, amine **105** urea **106** and unidentified byproducts as shown by ^{1}H NMR.

Isocyanate dimer; 7-Nitro-3-(5-nitropyridin-2-yl)-*2H*-pyrido[1,2-*a*][1,3,5]triazine-2,4(*3H*)-dione (92).[46] ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.45 (d, *J* 2.8 Hz, 1H, py'-H6), 9.18 (d, *J* 2.8 Hz, 1H, H6), 8.88 (dd, *J* 8.4, 2.8 Hz, 1H, py'-H4), 8.47 (dd, *J* 10.0, 2.8 Hz, 1H, H8), 7.86 (d, *J* 8.4 Hz, 1H, py'-H3), 7.32 (d, *J* 10.0 Hz, 1H, H9).

2-Amino-5-nitropyridine (105).[43] ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 8.84 (d, *J* 3.0 Hz, 1H, H6), 8.12 (dd, *J* 9.3, 3.0 Hz, 1H, H4), 7.54 (br s, 2H, -NH_2), 6.50 (d, *J* 9.3 Hz, 1H, H3).

1,3-Bis(5-nitropyridin-2-yl)urea (106).[46] ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.73 (br s, 2H, -NH-), 9.17 (d, *J* 2.7 Hz, 2H, H6), 8.63 (dd, *J* 9.3, 2.7 Hz, 2H, H4), 8.08 (d, *J* 9.3 Hz, 2H, H3).

Typical cycloaddition attempt from 5-nitropicolinoyl azide (99) and 4-(triethylsilyl)pyridin-3-yl trifluoromethanesulfonate (111). Acylazide **99** (24 mg, 0.124 mmol) and pyridyne precursor **111** (127 mg, 0.373 mmol) were dissolved in benzene-d_6 (4 mL), and the azeotrope was distilled off under reduced pressure. The solution was heated to reflux and kept stirring for 15 min, before it was allowed to cool to room temperature. Full conversion of acylazide **99** to isocyanate **91** (50%), isocyanate dimer **92** (43%) and amine **105** (7%), as well as unreacted triflate **111**, was observed by ^{1}H NMR. CsF was dissolved in MeCN-d_3 (5 mL) and benzene-d_6 (1 mL) under an argon atmosphere, and the ternary azeotrope was distilled off under reduced pressure. The *dry* CsF solution was added to the reaction mixture at 0 °C and the reaction mixture was stirred for 30 min before it was allowed to warm to room temperature and stirred for an additional 30 min. After removal of the solvent under reduced pressure a tarry and highly polar material was obtained. No products were isolated or identified by ^{1}H NMR from this material.

2-isocyanato-5-nitropyridine (91).[46] ^{1}H NMR (400 MHz, benzene-d_6): δ_H 8.63 (d, *J* 2.8 Hz, 1H, H6), 7.35 (dd, *J* 8.8, 2.8 Hz, 1H, H4), 5.79 (d, *J* 8.8 Hz, 1H, H3).

Isocyanate dimer; 7-Nitro-3-(5-nitropyridin–2-yl)-*2H*-pyrido[1,2-*a*][1,3,5]triazine-2,4(3*H*)-dione (92).[46] ^{1}H NMR (400 MHz, benzene-d_6): δ_H 8.88 (dd, *J* 2.8, 0.8 Hz, 1H, py'-H6), 8.40 (dd, *J* 2.8, 0.8 Hz, 1H, H6), 7.64 (dd, *J* 8.4, 2.8 Hz, 1H, py'-H4), 7.02 (dd, *J* 10.0, 2.8 Hz, 1H, H8), 6.71 (dd, *J* 8.4, 0.8 Hz, 1H, py'-H3), 6.11 (dd, *J* 10.0, 0.8 Hz, 1H, H9).

2-Amino-5-nitropyridine (105).[43] ^{1}H NMR (400 MHz, benzene-d_6): δ_H 8.80 (d, *J* 2.8 Hz, 1H, H6), 7.43 (dd, *J* 9.6, 2.8 Hz, 1H, H4), 5.16 (d, *J* 9.6 Hz, 1H, H3), 4.30 (br s, 2H, -NH_2).

4-(Triethylsilyl)pyridin-3-yl trifluoromethanesulfonate (111).[198] ^{1}H NMR (400 MHz, benzene-d_6): δ_H 8.71 (s, 1H, H1), 8.29 (d, *J* 4.4 Hz, 1H, H6), 6.85 (d, *J* 4.4 Hz, 1H, H5), 0.80 (m, 15H, -$Si(CH_2CH_3)_3$).

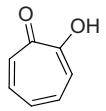
6 Reactive pyridylketones formed by Weinreb transformations

This chapter summarizes some of the results presented in Paper IX. Master of Science Svein Jacob Kaspersen and Master of Technology Alexander Nicolaisen are acknowledged for their contributions to this project.

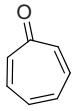
6.1 Background

Tropolones (**X**) and *Tropones* (**XI**, Scheme 27) have been of increasing interest in the past few years. Approximately 200 such materials occur in nature and these widespread natural products exhibit varied biological properties such as antibacterial, antifungal, antiviral and antitumor activities.[201] Tropolone (**X**) itself is bacteriostatic and bactericidal towards a wide range of bacterial species.[202] Other biological activities have been discovered and summarized.[203]

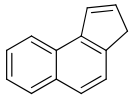
Scheme 27



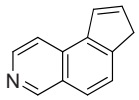
X
tropolone



XI
tropone



XII
3*H*-benzo[*e*]indene



XIII
7*H*-cyclopenta[*f*]isoquinoline

Cyclopentaphenanthrenes such as benzo[*e*]indene **XII** have been prepared and studied, due to the interesting properties of its corresponding, deprotonated carbanion.[204-206] The acidity and stability of such cyclopentadienide ions have been investigated in order to understand proton transfer as a physical and chemical phenomenon. 7H-Cyclopenta[*f*]isoquinoline (**XIII**) derivatives have been prepared and studied as DNA-interacting agents in cancer chemotheraphy.[207,208] A substituted cyclopenta[*f*]-isoquinoline derivative is a key intermediate in the synthesis of (±)-fredericamycin A, an antitumor antibiotic.[209,210]

6.1.1 Objective

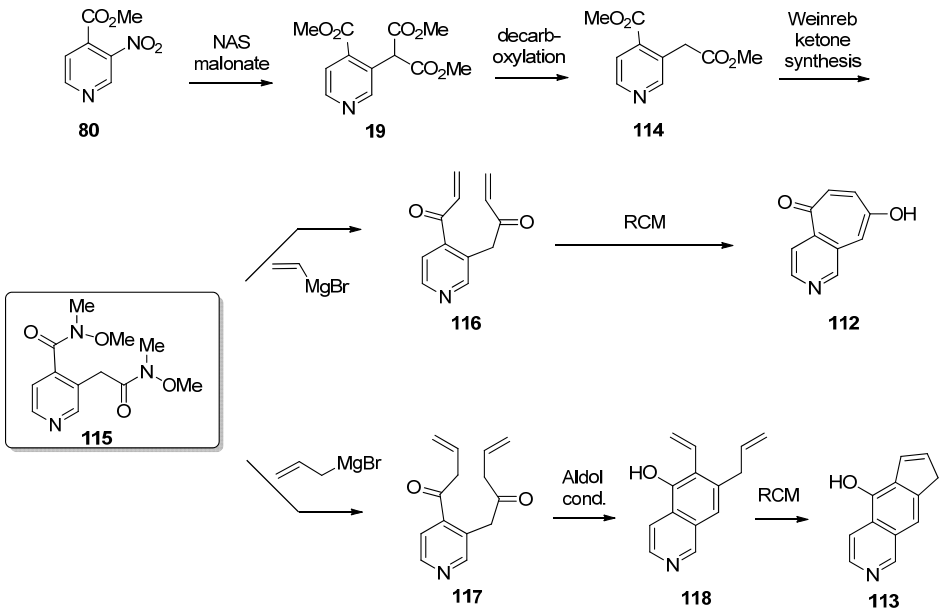
In reference to the biological activity, the therapeutic use and the generally interesting properties discussed above, it would be of interest to prepare new closely related heterocyclic analogues of tropolone (**X**) and 7*H*-cyclopenta[*f*]isoquinoline (**XIII**). The

fused heterocycles shown in Scheme 28, 8-hydroxy-5*H*-cyclohepta[*c*]pyridine-5-one (**112**) and 8*H*-cyclopenta[*g*]isoquinolin-5-ol (**113**), would therefore be interesting target compounds, due to their potential biological properties. We wanted to study the preparation of these new heterocyclic compounds.

6.1.2 Synthetic strategy

Tjosås and Fiksdahl have previously reported[51] the nucleophilic aromatic substitution (NAS) of the nitro group in 3-nitropyridyl carboxylate (**80**) with malonate to give 3-pyridylmalonate product **19**. By a modified Krapscho decarboxylation procedure, using MW irradiation, the homochinchomeric acid dimethyl ester **114** was obtained (Scheme 28).

Scheme 28



Our approach for the preparation of tropolone analogue **112** and cyclopenta[*g*]-isoquinolinol **113** was based on the formation of divinylketone **116** and diallylketone **117** from Weinreb's amide **115**. Ring-closing metathesis (RCM) of the vinyl-vinyl moiety of compound **116** would give the 7-membered cyclic product **112**. 7-Allyl-6-vinylisoquinoline product **118** would be obtained by an intramolecular regioselective aldol condensation of diallylketone **117**. Subsequent RCM of the vinyl-allyl moiety of compound **118** would give the tricyclic product **113**.

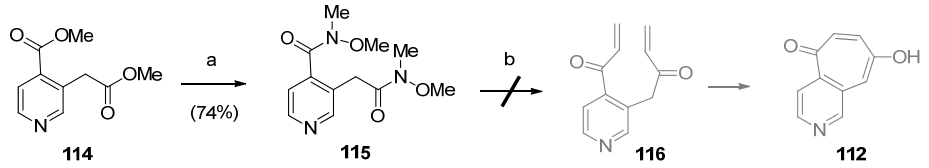
6.2 Results and discussion

Weinreb's amides, *N*-methoxy-*N*-methyl amides, are useful intermediates in organic synthesis since they react efficiently with organometallic species to produce ketones. The diester **114**, a less reactive carboxylic acid derivative, was readily converted to the Weinreb's amide **115** (74%), allowing the introduction of two amide groups by using the powerful Me_2AlCl/MeONHMe·HCl reagent system (Scheme 29).[185]

6.2.1 Studies on reactive pyridylvinylketones

Divinylketone **116** is an intermediate for the preparation of pyridoisotropolone **112**. Unfortunately, the vinylketone transformation of Weinreb's amide **115** to diketone **116** was not successful, probably due to the high reactivity of the pyridylvinylketone **116**. The reaction resulted in a tarry and poorly soluble material, and no products were isolated or identified (Scheme 29).

Scheme 29

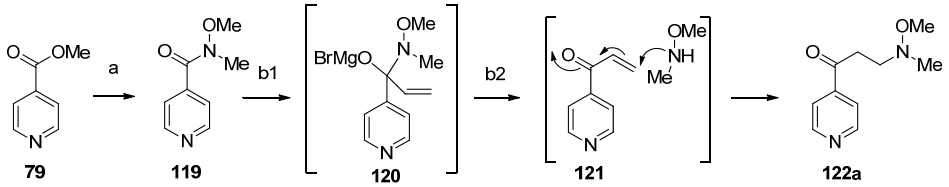


114 **115** **116** **112**

Reagents and conditions: (a) 1. Me_2AlCl, MeONHMe·HCl in CH_2Cl_2, 0 °C, 2. Borate buffer (pH 8); (b) 1. $CH_2CHMgBr$, THF, -78 °C, 1/2 h, 2. NH_4Cl.

To develop a practical preparation of reactive pyridylvinylketones and activated vinylketones in general, reaction of vinyl magnesium bromide with Weinreb's amide **119** (obtained from methyl isonicotinate **79**) was investigated (Scheme 30). By addition of excess of vinylMgBr to *N*-metoxy-*N*-methylamide **119**, vinylketone **121** was formed upon acidic work-up *via* formation of the tetrahedral intermediate **120**. The vinylketone **121** was not observed, but was directly trapped *in situ* by the amine leaving group during work-up. The corresponding Michael product **122a** was isolated in 70% yield. Direct synthesis of β-aminoketones from amides *via* sequential nucleophilic substitution/Michael reaction has been reported earlier.[211] Introduction of other *N*-nucleophiles is possible by trapping vinylketone **121** with amines, added to the reaction mixture.[212] These *N*-nucleophiles must compete with *N*-methyl-*N*-methoxyamine formed as a leaving group by the decomposition of the tetrahedral intermediate **120** into vinylketone **121**.

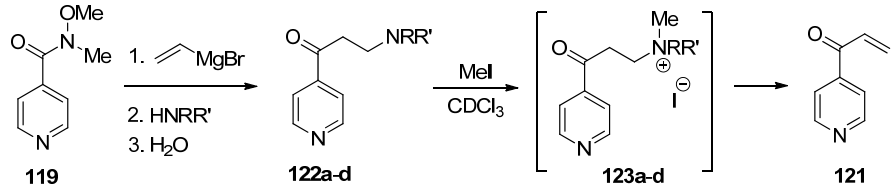
Scheme 30

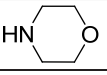


Reagents and conditions: (a) 1. Me_2AlCl, MeONHMe·HCl in CH_2Cl_2, 0 °C, 2. Borate buffer (pH 8); (b1) $CH_2CHMgBr$, THF, -78 °C, 1/2 h; (b2) NH_4Cl.

By introduction of dibutylamine, piperidine or morpholine to the reaction mixture before addition of water, the amine addition products **122b-d** (72-89%) were isolated (Table 2). No amine **122a** arising from Michael addition of *N*-methyl-*N*-methoxyamine to the ketone **121** was observed.

Table 2. Preparation of amines **122a-d**, and conversion to vinylketone **121** by reaction with methyl iodide.



Entry	Amine	Product	Isolated yield (%)	Product	Conversion[b] (%)
1[a]	HN(OMe)Me	**122a**	70	**121**	5
2	HN(*n*-Bu)$_2$	**122b**	72	**121**	100
3		**122c**	89	**121**	35
4		**122d**	72	**121**	55

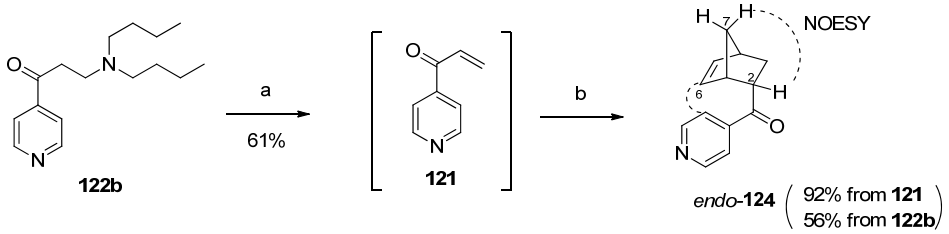
[a]The amine was not added, see Scheme 30. [b]The conversion to product **121** was determined by ^{1}H NMR after 10 h.

To enable the formation of a stable solution of the reactive pyridylvinylketone **121**, the isolated amine products **122a-d** were converted into quarternary ammonium intermediates **123a-d** by reaction with methyl iodide (Table 2). *In situ* amine

elimination afforded the desired vinylketone **121** in solution. We studied the elimination reaction by ^{1}H NMR spectroscopy and found that the dibutylamine intermediate **122b** gave full conversion to the vinylketone **121** in 10 hours. Low to moderate conversions of amines **122a, 122c** and **122d** (5-55%) into vinylketone **121** were observed.

To demonstrate the utility of the reactive pyridylvinylketone **121** in subsequent synthetic transformations, a pure and stable solution of vinylketone **121** (61%) in $CDCl_3$ was prepared, by repeated washing of the organic solution with water. The yield was determined based on 1,2,4,5-tetrachlorobenzene as internal standard. The vinylketone **121** in a $CDCl_3$ solution was treated with cyclopentadiene to undergo a Diels-Alder cycloaddition reaction (Scheme 31). The bicyclo[2.2.1]heptenyl product **124** was isolated in excellent yield (92% from vinylketone **121**; 56% from amine **122b**). As might be expected, the *endo* isomer was formed exclusively,[213] something which was confirmed by 2D NMR experiments. NOESY effects between H2 and H7, and between pyridine-H3/-H5 and H6, were observed, confirming the *endo* relationship. No traces of the *exo*-isomer could be observed.

Scheme 31



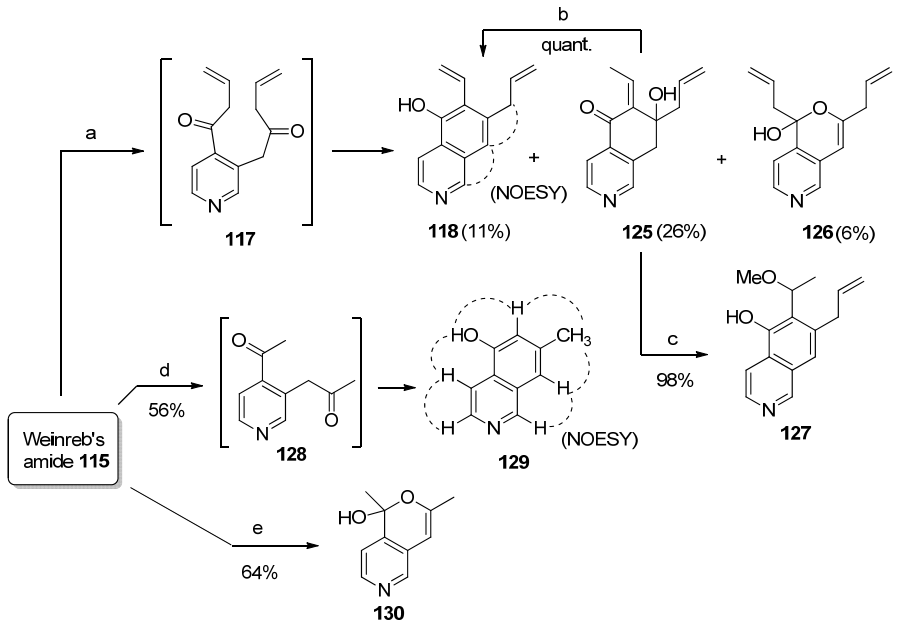
Reagents and conditions: (a) 1. MeI in $CDCl_3$, 12h, 2. Washed with H_2O, Ar-flush, addition of 1, 2, 4, 5-tetrachlorobenzen for quantification; (b) Cyclopentadiene, -10 °C, 2 h.

6.2.2 Studies on allylpyridylketones and methylpyridylketones

The reaction of Weinreb's amide **115** with allylmagnesium bromide did not result in the isolation of diallyl intermediate **117** (Scheme 32). The initially formed diallylketone **117** was transformed directly into a mixture of cyclization products and unidentified byproducts. Depending on the procedures and work-up conditions, different ratios of aldol condensated product **118**, ethylidene product **125** and hemiketal **126** were observed. Quenching with an NH_4Cl solution allowed for the isolation of phenol product **118** (11%), formed by intramolecular aldol condensation of diketone **117**, and ethylidene product **125** (26%). The hemiketal **126** (6%), formed by *O*-acylation of the most stable enolate of diketone **117** was also isolated. The hemiketal **126** was later

isolated in higher yield (21%) by quenching with an ice-cold solution of NH_4Cl. We were not able to find conditions that allowed for complete and direct conversion to the desired product **118** from Weinreb's amide **115**. Separate experiments verified that elimination of water and complete aromatisation of **125** into **118** could be achieved by treatment of **125** in $CDCl_3$ with *p*-TsOH for 10 hours. Alternative treatments with HCl (1-5 M) or NaOH (3-5 M) were not successful, mainly affording the elimination product without any ethylidene-vinyl isomerisation. The isolation of methoxy-product **127** by conjugated addition of a methoxy group to the exocyclic double bond in product **125** supported the keto-ethylidene structure of **125**. The isolation of small amounts of compound **118** was laborious, and the compound was never isolated in sufficient amounts to test a final RCM for the preparation of product **113** properly. Initial, small scale (5-20 mg) experiments with Grubbs' 1st and 2nd generation catalysts, conducted in either benzene, CH_2Cl_2 or toluene under reflux, gave no conversion of the starting compound **118**.

Scheme 32



Reagents and conditions: (a) 1. CH_2CHCH_2MgBr, THF, -78 °C – rt, 2. NH_4Cl; (b) *p*-TsOH (cat.), $CDCl_3$, rt, 10 h; (c) NaOMe in MeOH, rt, overnight; (d) MeMgBr, THF, -78 °C – rt, 2h, 2. H_2O, 3. Na_2CO_3; (e) 1. MeMgBr, THF, -78 °C - rt, 3h, 2. NH_4Cl.

The dimethyldiketone **128** (Scheme 32) was selected as a less complex analogous compound for studying the transformation of Weinreb's amide **115**. Reacting amide

115 with MeMgBr and subsequent acidic work-up afforded neither diketone **128** nor the corresponding aldol product **129**. The less stable hemiketal **130** (64%) was obtained as the main product. In particular ^{13}C NMR of product **130** was useful for the structure elucidation of the diallylhemiketal product **126**. Such cyclocondensations are well known from the preparation of 2*H*- and 4*H*-pyran natural product from 1,5-diketone precursors.[214-216] The isoquinolinol product **129** (56%), an analogue to product **118**, was obtained by quenching the reaction mixture with water and subsequent alkaline treatment of the crude mixture. The isomeric compound, 6-methylquinolin-8-ol, has been used in the preparation of semi-synthetic β-lactams[217] and hair dyes.[218]

To summarize, a method to enable the preparation of the reactive vinylpyridylketone **121** from Weinreb's amide **114** was developed. The utility of the reactive vinylketone **121** in further synthesis was demonstrated by its ability to undergo a Diels-Alder cycloaddition reaction. Transformation of Weinreb's amide **115** into diallylketone **117** formed aldol cyclization products **118** and **125** and hemiketal cyclization product **126** directly. The analogous dimethyldiketone **128**, forming hemiketal **130** and aldol cyclization product **129**, was chosen as a less complex analogous product to study the transformation of Weinreb's amide **115.**

The studies on reactive pyridylketones are fully described in Paper IX. The formation of some over-alkylated products obtained from the diester **114** by reaction with allylMgCl was performed by Master of Technology Alexander Nicolaisen and is described therein.

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Paper I

Vegar Stockmann and Anne Fiksdahl

Preparation of new pyrido[3,4-*b*]thienopyrroles and pyrido[4,3-*e*]thienopyridazines

Tetrahedron **2008**, *64*, 7626.

Tetrahedron 64 (2008) 7626–7632

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Preparation of new pyrido[3,4-*b*]thienopyrroles and pyrido[4,3-*e*]-thienopyridazines

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ARTICLE INFO

Article history:
Received 22 February 2008
Received in revised form 29 April 2008
Accepted 15 May 2008
Available online 18 May 2008

Keywords:
Pyrido[3,4-*b*]thieno[2,3-*d*]pyrrole
Pyrido[3,4-*b*]thieno[3,2-*d*]pyrrole
Pyrido[4,3-*e*]thieno[2,3-*c*]pyridazine
Pyrido[4,3-*e*]thieno[3,2-*c*]pyridazine
Suzuki cross coupling
Diazotization
Diazocoupling
Azide
Nitrene
Thermal decomposition

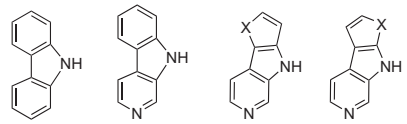
ABSTRACT

Two new types of pyrido-fused tris-heterocycles (**1a**,**b** and **2a**,**b**) have been prepared from 3-amino-pyridine in five/six steps. A synthetic strategy for the preparation of the novel pyrido[3,4-*b*]thieno[2,3- and 3,2-*d*]pyrroles (**1a**,**b**) and pyrido[4,3-*e*]thieno[2,3- and 3,2-*c*]pyridazines (**2a**,**b**) has been studied. The Suzuki cross coupling of the appropriate 2- and 3-thienoboronic acids (**3**,**4**) and 4-bromo-3-pyridylpivaloylamide (**9**) afforded the biaryl coupling products (**10**,**11**) in high yields (85%). Diazotization of the hydrolysed (2-thienyl)-coupling product (**12**) and azide substitution gave the 3-azido-4-(2-thienyl)pyridine intermediate (72%, **14**). 3-Azido-4-(3-thienyl)pyridine (**15**) was prepared by exchanging the previous order of reactions. The desired β-carboline thiophene analogues (**1a**,**b**) were obtained via the nitrene by thermal decomposition of the azido precursors (**14**,**15**). By optimising conditions for intramolecular diazocoupling, the corresponding pyridazine products (72–83%, **2a**,**b**) were afforded.

1. Introduction

1.1. Background

β-Carbolines (**II**, Scheme 1) are naturally occurring alkaloids that exhibit diverse biological and pharmacological activities. The β-carboline ring structure is thus incorporated into many natural products and pharmaceuticals. Numerous studies of natural occurrence, identification and isolation of β-carboline derivatives have been reported and studies of properties, biological and pharmacological effects of β-carboline alkaloids and derivatives have been carried out for several decades. Some of the most recent reports include studies of the antitumor/cytotoxic,[1] anticancer,[2] antimalaria,[3] antioxidant,[4] free radical scavenging and antithrombotic activities.[5] β-Carbolines have also been studied because of the neuroprotection[6] and photosensitiser abilities[7] as well as for treatment of ophthalmic/eye disorders.[8] β-Carbolines are *N*-analogues of carbazoles (**I**, Scheme 1), which are incorporated into a number of pharmaceutical agents as well. Both the Carvedilol[9] and the Carazolol[10] β-blockers are based on the carbazole tricyclic skeleton. By replacing the phenyl-ring of **II** by five-ring heterocycles, the novel thieno-, furano- or pyrrolo-β-carboline analogues (**III**, Scheme 1) would be constructed.



I carbazole **II** β-carboline **III** X = S, O, NH β-carboline analogues

Scheme 1.

Pyridazine (Scheme 2) compounds have also been shown to be biologically active and the pyridazine moiety is incorporated in a series of pharmaceuticals. Cinnolines (**IV**, Scheme 2)[11] are important intermediates in the preparation of the antidepressant Binodaline[12] and the antibiotic Cinoxacin.[13] A series of substituted benzo[*c*]cinnolines (**IVa**) have herbicidal activity,[14] while others are found to be mutagenic substances,[15] being identified as organic aza-heterocyclic pollutants.[16] The corresponding *N*-analogues pyrido[3,4-*c*]cinnoline (**IVb**) ring structure has also been reported.[17] Pyridopyridazines (**V**) have been studied for preventing and

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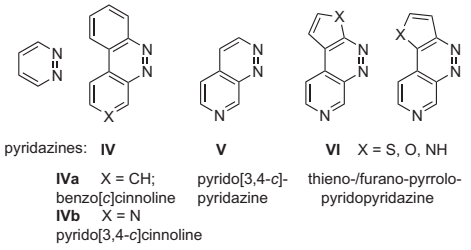
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.05.062

treating atherosclerosis[18] and have been used for the preparation of antiviral agents.[19] Structure **VI** represents potential five-ring-fused heterocyclic analogues.

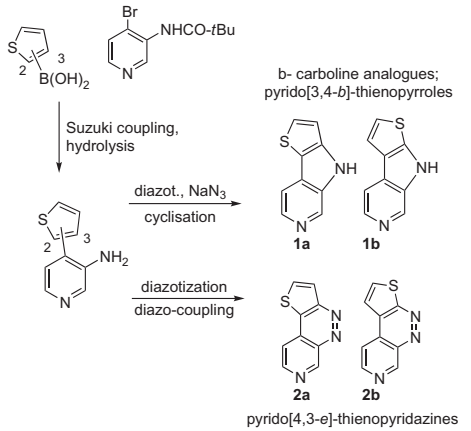


Scheme 2.

1.2. Objective

Referring to the biological activity, the therapeutic use and the generally interesting properties discussed above, it would be of interest to prepare new closely related heterocyclic analogues of both *β-carbolines* (**III**, Scheme 1) and fused *pyridazines* (**VI**, Scheme 2). Heterocycle-fused analogues of benzo-fused heterocycles may in general offer some advantages from a medicinal chemistry point of view, since the new heteroatom may provide better water solubility by offering an additional site for protonation or salt formation or it might enhance intermolecular interactions by formation of an additional hydrogen bond to target proteins. Many drugs are derived from thiophene. Bioisosteric effects have been observed, since the pharmacological effect of the thienyl moiety often is similar to phenyl or benzyl.[25,26]

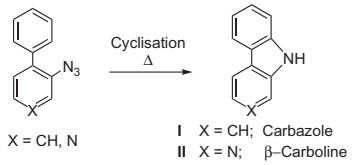
The thienyl-fused heterocycles shown in Scheme 3, the pyrido[3,4-*b*]thienopyrroles (**1a**,**b**) and the pyrido[4,3-*e*]thienopyridazines (**2a**,**b**), would therefore be promising target compounds, due to their potential biological properties. We wanted to study the preparation of these heterocyclic compounds.



Scheme 3.

1.3. Synthetic strategy

The synthetic preparation of β-carbolines has previously been based on different strategies. The most frequently used methods are, respectively, the reductive cyclisation of 3-nitro-4-phenylpyridines with $P(EtO)_3$[20] and the direct cyclisation of 3-azido-4-phenylpyridine by photolysis[21] or thermal decomposition[22] via the nitrene (Scheme 4). The nature of the aryl groups affects the cyclisation reactivity. The decomposition of biphenyl azides (X=CH) is known to afford the carbazoles (**I**) in high yields,[23,24] while the introduction of pyridine azide in these reactions reduces the reactivity towards cyclisation and the corresponding heterocyclic phenylpyridine azide produces β-carboline (**II**, X=N) in significantly lower yield.[25] Attempts to improve the yields of β-carboline by Lewis acid thermal cyclisation have met with no success.



Scheme 4.

The lower yield obtained for β-carboline (**II**, Scheme 4) compared to carbazole (**I**), may be caused by the electron-deficient character of the pyridine moiety. To improve the reactivity and compensate for the effect of the pyridine-ring, we wanted to replace the phenyl group in the biaryl system of the precursor by more electron-rich heterocyclic groups, such as five-ring heterocycles (thiophene/furan/pyrrole) to study whether more reactive biaryl azido-intermediates could be obtained in order to give five-ring β-carboline analogues (**III**).

In the present work, we examined the preparation of the new thieno-β-carboline analogue compounds (**1a**,**b**) shown in Scheme 3. These pyrido[3,4-*b*]thienopyrroles products can be prepared from 3-amino-4-bromopyridine by palladium catalysed Suzuki cross-coupling with suitable 2-/3-thiphene boronic acids followed by diazotization, azide substitution and thermal decomposition to afford the new thieno-β-carboline analogue products (**1a**,**b**).

This strategy would also give access to the novel pyrido[3,4-*c*]thienopyridazines **2a**,**b** by intramolecular diazocoupling of the diazonium intermediate.

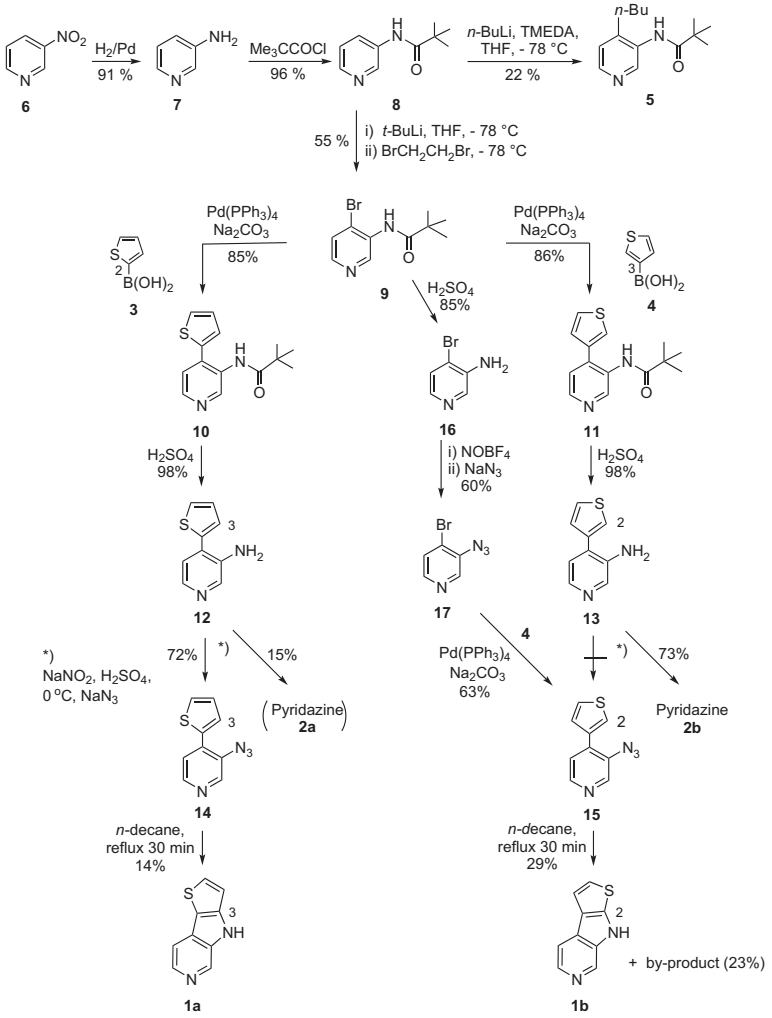
Our results for the preparation of the new potential biologically active pyridothienopyrroles (**1a**,**b**) and pyridothienopyridazines (**2a**,**b**) are discussed below.

2. Results and discussion

2.1. Intermediates

The synthetic sequences for the preparation of pyrido[3,4-*b*]-thieno[2,3-/3,2-*d*]pyrroles **1a**,**b** and pyrido[4,3-*e*]thieno[2,3-/3,2-*c*]-pyridazines **2a**,**b** are presented in Scheme 5. These two new groups of tricyclic heterocycles were prepared from 3-nitropyridine (**6**) through seven- and six-step pathways. Nitropyridines are now readily available through an improved nitration method[26,27] and an investigation of the chemistry of nitropyridines is in progress in our laboratories.

3-Aminopyridine (**7**) and the pivaloyl amide intermediate (**8**)[28] were obtained in high yields by nitro-reduction (91%) followed by derivatisation with pivaloyl chloride (96%). Pivaloylaminopyridines are known to undergo regioselective electrophilic substitution by *ortho*-lithiation[29] and the 4-bromo-3-amido compound **9** was prepared from **8**.[30] However, by using the *n*-BuLi/TMEDA method for lithiation, substantial quantities (22%) of the Ziegler alkylation product (**5**) was formed,[31] caused by nucleophilic attack at C-4 by *n*-BuLi. This problem has been reported by others as well.[32] The problem was avoided by using *t*-BuLi and the 4-bromo-3-



Scheme 5.

aminopyridine derivative **9** was isolated (55%) after lithiation of **8** and subsequent reaction with the electrophilic ethylene dibromide.

In Suzuki couplings reactions, (i) electron-deficient aryl halides and (ii) electron-rich boronic acids are the substrates of choice, since those compounds are more reactive than the contrary in, respectively, (i) the oxidative addition and (ii) the transmetallation steps. The Suzuki coupling of 4-bromopyridine (**9**) with commercially available 2- and 3-thienylboronic acids (**3**,**4**) afforded the corresponding thien-2-/3-ylpyridine coupling products **10** and **11** in high yields (85–86%). The yields were not altered by reducing the amount of $Pd(PPh_3)_4$ from 5 to 2.5 mol % or the reaction time (12–6 h). Acidic hydrolysis afforded the aminopyridine intermediates **12** and **13** in quantitative yields.

2.2. Pyrido[3,4-*b*]thienopyrroles (1a,b)

Diazotisation of aminopyridine **12** and subsequent nucleophilic substitution of the diazonium group with azide afforded the azide product **14** in 72% yield. By the corresponding reaction of thien-3-yl intermediate **13**, the azide product **15** was not observed at all, due to the competing exclusive formation of the intramolecular diazo-coupling compound (73%, **2b**) (see Section 2.3 below). By exchanging the order of the Suzuki coupling, the hydrolysis and diazotisation steps described above, an alternative method was used for the preparation of the azide product **15** (Scheme 5). Hydrolysis of intermediate **9** (85%) followed by $NOBF_4$ diazotisation/azide substitution (60%) and subsequent Suzuki coupling (63%) yielded the azide **15** via intermediates **16** and **17**.

Cyclisation by thermal decomposition of azides **14** and **15** via the nitrenes, afforded the desired β-carboline analogues **1a**,**b** by C–H insertion into the 3- and 2-positions of thethiophene, respectively. As expected from the higher reactivity of the 2-position of the thiophene compared to the 3-position, an increased yield was obtained by cyclisation of azide **15** to give **1b** (29%) compared to **14** for the formation of **1a** (14%). However, the yields were reproducibly low and was not changed or improved by altering the reaction time (10 min—5 days), the solvent (*n*-nonane, *n*-decane, and undecane), the reflux temperature (150–195 °C) or by

introducing a Lewis acid (Ti(O–*i*-Pr)$_4$). Attempts at performing the cyclisation by microwave irradiation offered no advantages compared to conventional heating.

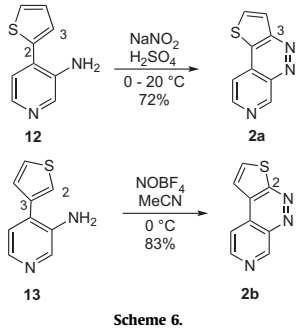
The thermal decomposition of azide **15** also afforded an additional by-product. This new compound was isolated in equivalent amounts (23%) as the desired cyclisation product **1b** but was considerably less polar. The nature of this compound is being investigated.[43] In all reactions, small amounts of the corresponding primary amine (<5% for azide **14** and <1% for azide **15**) and tarry inseparable products were formed. It is known that such competing reactions may take place when ring closure is too difficult under the conditions employed, since the nitrene may abstract hydrogens from the solvent or similar molecules. Such azide reductions are also reported to occur together with tar formation.[33–36]

X-ray analysis of the tricyclic product **1b** reveal that there are 16 molecules in an unusual cell packing structure.[37]

The present results show that replacing the phenyl group in the biaryl azide precursor of β-carboline (Scheme 4) by the more electron-rich thiophene moiety did not improve or compensate for the lower reactivity of the electron-deficient pyridine substrates.[25] Thus, similar reactivity of the phenylpyridyl and thienopyridyl azides (**14**,**15**) to give β-carboline and the thiophene analogues has been demonstrated.

2.3. Pyrido[4,3-*e*]thienopyridazines (2a,b)

Due to the electron-rich and electron-deficient character of the thienyl and pyridine moieties, respectively, compounds **12** and **13** represent appropriate intermediates for the formation of intramolecular diazocoupling pyridazine products. Even if electrophilic substitution at the 3-position of thiophene is known to be negligible, minor amounts (15%) of thienopyrido[3,4-*c*]pyridazine **2a** was isolated from the diazotisation and azide substitution reaction of aminopyridine **12** (Scheme 5), aiming at the azide product **14** (72%, Section 2.2). However, pyridazine product **2b** was exclusively formed (73%) from **13**. Pyridazine **2b** is a regioisomer of **2a**, formed by electrophilic substitution at the highly reactive 2-position of the thiophene **13**. As expected, no product due to reaction in the thienyl-4-position of **13** was observed. In the absence of azide nucleophile, in order to optimise diazocoupling, the pyridazine products **2a** and **2b** were afforded in 72% and 83% yields, respectively (Scheme 6). Their structures were confirmed by X-ray analysis.[38,39]



Scheme 6.

The higher reactivity of the 2-position compared to the 3-position of the thiophene was also demonstrated by the fact that strongly acidic conditions ($NaNO_2/H_2SO_4$, see Scheme 6) were definitely required for the conversion of thien-2-yl **12** to **2a** to take place. The strong acid would activate the diazonium group by protonation of the pyridine moiety. As shown in Scheme 6, no such activation was needed for diazocoupling of the thien-3-yl **13** to give **2b**, since this reaction also took place using $NOBF_4$/MeCN. Due to the electron-deficient and hence more reactive thienopyridine diazonium ion, the obtained yields of the present pyridazines **2a**,**b** are considerably higher than reported for the corresponding thienophenyl diazonium analogues for the formation of thieno[3,2- and 2,3-*c*]cinnolines (13–69%).[40]

3. Conclusion

Two new types of pyrido-fused tris-heterocycles have been prepared from 3-aminopyridine in five/six steps. The novel β-carboline analogues pyrido[3,4-*b*]thieno[2,3/3,2-*d*]pyrroles (**1a**,**b**) have been prepared by the Suzuki—nitrene approach. Additionally, this diazonium intermediate pathway allowed the synthesis of the new pyrido[4,3-*e*]thieno[2,3/3,2-*c*]pyridazines (**2a**,**b**) products by diazocoupling. The preparation of analogous furan and pyrrole products is now in progress in our laboratories.

4. Experimental

4.1. General

Chemicals: 2- and 3-Thiophene boronic acid, *n*-BuLi, *t*-BuLi (Sigma–Aldrich), $NaNO_2$ (Merck), BF_4NO, $C_2H_4Br_2$, $Pd(PPh_3)_4$ (Fluka). *Solvents*: Pro analysi quality. THF and ether were distilled from sodium metal and benzophenone and used directly. All moisture or air sensitive reactions were performed under nitrogen atmosphere in pre-dried glassware. Flash column chromatography; SiO_2 (SDS, 60 Å, 40–63 μm). ^1H and ^{13}C NMR: Bruker Avance DPX 300 and 400 MHz spectrometers, chemical shifts are reported in parts per million downfield from TMS. *J* values are given in hertz. MS: Finnigan MAT 95 XL mass spectrometer (EI, 70 eV). IR spectra were obtained with a Nicolet 20SXC FT-IR spectrophotometer, recorded using a Smart Endurance reflexion cell, unless film or KBr are specified. All melting points are uncorrected, measured on a Stuart apparatus. Elemental analyses were done by the Laborator Beller/Matties, Göttingen, Germany. 3-Nitropyridine (**6**) was prepared by nitration of pyridine.[26,27] 3-Aminopyridine (**7**)[41] was prepared by hydrogenation of **6**, according to the literature[42] or purchased from Aldrich and used directly.

4.2. Pyrido[3,4-*b*]thieno[2,3-*d*]pyrrole (1a)

Thermal cyclisation of azide **14** was carried out by heating a stirred solution of **14** (141 mg, 0.697 mmol) in *n*-decane (50 mL) to above 170 °C. The mixture was kept stirring at reflux until full conversion of azide **14** (approx. 30 min, monitored by TLC). The reaction was allowed to cool to room temperature and the decane was distilled off. Flash chromatography (gradient; 0–10% MeOH/CH_2Cl_2) afforded **1a** as a white solid (17 mg, 14%), pure by NMR; R_f 0.20 (10% MeOH/CH_2Cl_2); mp 217–218 °C; ^1H NMR (300 MHz, DMSO-d_6) δ_H: 11.81 (1H, br s, NH), 8.83 (1H, s, *J* 0.9, pyr-H2), 8.20 (1H, d, *J* 5.4, pyr-H6), 7.84 (1H, d, *J* 5.4, thieno-H5), 7.74 (1H, dd, *J* 5.4, 0.9, pyr-H5), 7.29 (1H, d, *J* 5.4, thieno-H4); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.98 (1H, s), 8.31 (1H, d, *J* 5.6), 7.67 (1H, d, *J* 5.6), 7.60 (1H, d, *J* 5.2), 7.17 (1H, d, *J* 5.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 148.0 (thieno-C3), 137.8 (pyr-C2), 135.0 (pyr-C6), 133.0 (thieno-C4), 132.3 (pyr-C3), 127.8 (pyr-C4), 116.6 (thieno-C2), 113.4 (pyr-C5), 111.9 (thieno-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 2919, 2851, 1609, 1459, 1344, 1280, 1091, 1053, 986, 817, 806, 797, 762, 707, 667 cm^{-1}; MS *m*/*z* (%): 174 (M^+, 100), 149 (12), 129 (4), 87 (5), 57 (7), 43 (4), 28 (25); HRMS calcd for $C_9H_6N_2S$: 174.0252; obsd 174.0249.

4.3. Pyrido[3,4-*b*]thieno[3,2-*d*]pyrrole (1b)

The title compound was prepared from azide **15** (150 mg, 0.742 mmol) in *n*-decane (50 mL) as described above for the formation of **1a** from **14**. Product **1b** was obtained as a light grey solid (38 mg, 0.218 mmol, 29%), pure by NMR. This procedure also afforded a less polar by-product (23%) after flash chromatography.[43] Compound **1b**: R_f 0.19 (10% MeOH/CH_2Cl_2); mp 225–226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 12.02 (1H, br s, NH), 8.80 (1H, s, *J* 5.4, pyr-H2), 8.21 (1H, d, *J* 5.4, pyr-H6), 7.76 (1H, d, *J* 5.4, pyr-H5), 7.47 (1H, d, *J* 5.4, thieno-H5), 7.17 (1H, d, *J* 5.4, thieno-H4); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 145.2, 138.8, 138.2, 133.8, 125.4, 122.9, 119.2, 117.9, 113.4; IR (KBr) ν_{max}: 3102, 2586, 1608, 1575, 1491, 1477, 1276, 1110, 1035, 805, 715, 709, 667, 640, 594 cm^{-1}; MS *m*/*z* (%): 174 (M^+, 18), 149 (9), 109 (19), 95 (31), 69 (42), 57 (48), 44 (100); HRMS calcd for $C_9H_6N_2S$: 174.0252; obsd 174.0250. Anal. Calcd for $C_9H_6N_2S$: C, 62.05; H, 3.47; N, 16.08; S, 18.40. Found: C, 61.95; H, 3.40; N, 15.98; S, 18.26. X-ray analysis.[37]

4.4. Pyrido[4,3-*e*]thieno[3,2-*c*]pyridazine (2a)

To a stirred solution of amine **12** (106 mg, 0.602 mmol) in H_2SO_4 (10 mL) at 0 °C was added $NaNO_2$ (62 mg, 0.899 mmol) in H_2O (6 mL) dropwise during 30 min. The reaction was kept stirring for 30 min at 0 °C and then allowed to warm to room temperature and stirred overnight. The reaction was added to NaOH (90 mL, 5 M) and ice. The aqueous solution was extracted with CH_2Cl_2 (3×30 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) affording **2a** as a white solid (81 mg, 72%), pure by NMR; **2a** (15% yield) was also isolated from a 15:72% mixture with **14**, (see preparation of **14** below). Compound **2a**: R_f 0.30 (4% Et_3N in EtOAc/pentane (2:1)); mp 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.12 (1H, d, *J* 0.8, pyr-H2), 8.89 (1H, d, *J* 6.0, pyr-H6), 8.23 (1H, d, *J* 5.6, thieno-H5), 7.99 (1H, d, *J* 5.6, thieno-H4), 7.93 (1H, dd, *J* 6.0, 0.8, pyr-H5); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 156.4 (thieno-C3), 156.1 (pyr-C2), 147.8 (pyr-C6), 139.9 (pyr-C3), 131.2 (thieno-C4), 130.2 (thieno-C2), 126.1 (thieno-C5), 125.7 (pyr-C4), 115.3 (pyr-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 3085, 1603, 1414, 1354, 1331, 1279, 1243, 1234, 1130, 1098, 991, 867, 829, 811, 804, 743, 690 cm^{-1}; MS *m*/*z* (%): 187 (M^+, 100), 176 (59), 149 (33), 132 (91), 57 (78), 41 (52); HRMS calcd for $C_9H_5N_3S$: 187.0204; obsd 187.0201. X-ray analysis.[38]

4.5. Pyrido[4,3-*e*]thieno[2,3-*c*]pyridazine (2b)

To a stirred solution of $NOBF_4$ in MeCN (5 mL) at 0 °C, amine **13** (116 mg, 0.658 mmol) in MeCN (5 mL) was added over 15 min. The reaction was kept stirring for 30 min at 0 °C before NaOH (15 mL, 5 M) was added. The crude product obtained after extraction with CH_2Cl_2 (3×20 mL), drying over Na_2SO_4 and concentration under reduced pressure was purified by flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) to give the product **2b** as a yellow solid (102 mg, 83%), pure by NMR; R_f 0.25 (4% Et_3N in EtOAc/pentane (2:1)); (alternatively, **2b** was exclusively formed in 73% yield from **13** by the reaction conditions described for the formation of **14** and minor amounts of **2a** below); mp 203–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.09 (1H, s, pyr-H2), 8.91 (1H, d, *J* 5.6, pyr-H6), 8.13 (1H, d, *J* 5.6, thieno-H5), 8.08 (1H, dd, *J* 5.6, 0.8, pyr-H5), 7.95 (1H, d, *J* 6.0, thieno-H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 161.8 (thieno-C2), 155.6 (pyr-C2), 147.7 (pyr-C6), 141.0 (pyr-C3), 134.2 (thieno-C5), 126.4 (thieno-C3), 125.2 (pyr-C4), 119.3 (thieno-C4), 115.3 (pyr-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 3039, 1604, 1429, 1389, 1337, 1277, 1260, 1198, 1141, 1079, 1025, 945, 839, 823, 809, 756, 678 cm^{-1}; MS *m*/*z* (%): 187 (M^+, 100), 159 (7), 132 (45), 44 (22), 28 (8); HRMS calcd for $C_9H_5N_3S$: 187.0204; obsd 187.0203. X-ray analysis.[39]

4.6. 4-Butyl-3-pivaloylaminopyridine (5)[44]

The title compound was formed[31,32] in a reaction of **8**, TMEDA (tetramethyl-1,2-diaminoethane) and *n*-BuLi in THF, and was isolated as a yellow solid (22%) by flash chromatography (4% Et_3N in EtOAc/pentane (2:1)), pure by NMR; R_f 0.26 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.89 (1H, s, H1), 8.34 (1H, d, *J* 4.8, H6), 7.21 (1H, br s, NH), 7.12 (1H, d, *J* 4.8, H5), 2.55 (2H, t, *J* 8.0, 1′-CH_2), 1.59 (2H, m, 2′-CH_2), 1.40 (2H, m, 3′-CH_2), 1.37 (9H, s, *t*-Bu), 0.96 (3H, t, *J* 7.6, 4′-CH_3); MS *m*/*z* (%): 234 (M^+, 66), 192 (33), 150 (17), 121 (23), 108 (42), 107 (19), 85 (12), 57 (100).

4.7. *N*-(Pyridin-3-yl)pivalamide (8)[28]

The title compound was prepared from amine **7** (1.37 g, 14.6 mmol) as described elsewhere.[29] Product **8** was isolated as a slightly yellow solid (2.50 g, 96%), pure by NMR; R_f 0.25 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.58 (1H, d, *J* 2.8, H2), 8.32 (1H, dd, *J* 4.8, 1.2, H6), 8.15 (1H, ddd, *J* 8.4, 2.8, 1.2, H4), 7.80 (1H, br s, NH), 7.25 (1H, dd, *J* 8.4, 4.8, H5), 1.32 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 177.3 (C═O), 145.0 (C6), 141.5 (C2), 135.0 (C3), 127.6 (C4), 123.5 (C5), 39.6 (quart-C), 27.4 (CH_3); NMR assignments are based on HSQC experiments; IR ν_{max}: 3172w, 2968w, 1677s, 1584s, 1537s, 1475s, 1420s, 1397s, 1325s, 1282s, 1264s, 1162s, 801s, 747m, 704s cm^{-1}; MS *m*/*z* (%): 178 (M^+, 6), 94 (20), 85 (10), 78 (4), 67 (5), 57 (100), 41 (25), 39 (16); HRMS calcd for $C_{10}H_{14}N_2O$: 178.1106; obsd 178.1108.

4.8. *N*-(4-Bromo-3-pyridinyl)-2,2-dimethylpropanamide (9)[30]

t-BuLi (61 mL, 103.8 mmol, 1.7 M in pentane) was added dropwise in 30 min to a stirred solution of **8** (7.40 g, 41.51 mmol) in THF (60 mL) and ether (110 mL) at −78 °C. The reaction was stirred for 30 min at −78 °C, 30 min at −20 °C and 1.5 h at room temperature. The reaction was cooled to −78 °C and ethylene dibromide (10.73 mL, 124.5 mmol) was added dropwise during 30 min. The mixture was allowed to heat to room temperature and stirred overnight before water (100 mL) was added. Extraction and flash chromatography (1:1 EtOAc/pentane) afforded **9** as a light yellow solid (5.85 g, 55%), pure by NMR; R_f 0.28 (EtOAc/pentane (1:1)); mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.53 (1H, s, H2), 8.17 (1H, d, *J* 5.2, H6), 7.83 (1H, br s, NH), 7.50 (1H, d, *J* 5.2, H5), 1.37 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 176.5 (C═O), 145.2 (C6), 143.5 (C2), 133.3 (C3), 127.0 (C5), 123.3 (C4), 40.1 (quart-C), 27.6 (CH_3); NMR assignments are based on HSQC experiments; IR ν_{max}: 3282m, 2965w, 1654s, 1568s, 1555s, 1495s, 1466s, 1398s, 1289m, 1174s, 1074m, 1064m, 862m, 805s, 669s cm^{-1}; MS *m*/*z* (%): 256 (M^+, 6), 172 (14), 85 (22), 57 (100), 41 (25), 39 (9); HRMS calcd for $C_{10}H_{13}BrN_2O$: 256.0211; obsd 256.0209.

4.9. *N*-(4-(Thien-2-yl)pyridin-3-yl)pivalamide (10)

A solution of **9** (2.00 g, 7.78 mmol) and $Pd(PPh_3)_4$ (419 mg, 0.363 mmol) in toluene (15 mL) was stirred and added Na_2CO_3 (7.5 mL, 2 M) and 2-thienylboronic acid (1.19 g, 9.30 mmol) in MeOH (5 mL).[45] The reaction was heated to 80–90 °C overnight. The reaction was allowed to cool to room temperature before CH_2Cl_2 (60 mL) and NH_3 (4 mL, concd) in Na_2CO_2 (40 mL, 2 M) was added. The white/yellow crude product, obtained by extraction, was purified by flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) to give **10** as a white solid (1.72 g, 6.61 mmol, 85%), pure by NMR; R_f 0.31 (4% Et_3N in EtOAc/pentane (2:1)); mp/decomp. 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.43 (1H, s, pyr-H2), 8.39 (1H, d, *J* 4.8,

pyr-H6), 7.72 (1H, br s, NH), 7.53 (1H, dd, *J* 4.8, 1.2, thieno-H5), 7.31 (1H, dd, *J* 4.8, pyr-H5), 7.26 (1H, dd, *J* 3.6, 1.2, thieno-H3), 7.20 (1H, dd, *J* 4.8, 3.6, thieno-H4), 1.25 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 176.5 (C=O), 145.3 (pyr-C6), 144.6 (pyr-C2), 136.3 (thieno-C2), 132.6 (pyr-C4), 131.6 (pyr-C3), 128.1 (thieno-C5), 128.0 (thieno-C4), 127.8 (thieno-C3), 123.9 (pyr-C5), 39.8 (CMe_3), 27.4 (C(CH_3)$_3$); IR ν_{max}: 3094, 2966, 1670, 1603, 1555, 1512, 1475, 1429, 1410, 1305, 1164, 823, 806, 746, 729, 704, 689 cm^{-1}; MS *m*/*z* (%): 260 (M^+, 90), 175 (42), 149 (14), 131 (16), 85 (16), 57 (100), 43 (26), 41 (17), 29 (10); HRMS calcd for $C_{14}H_{16}N_2OS$: 260.0983; obsd 260.0987. Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.58; H, 6.19; N, 10.76; S, 12.32. Found: C, 64.62; H, 6.20; N, 10.71; S, 12.20.

4.10. *N*-(4-(Thien-3-yl)pyridin-3-yl)pivalamide (11)

The title compound was prepared from **9** (5.02 g, 19.5 mmol) and Pd(PPh_3)$_4$ (1.13 g, 0.977 mmol) in toluene (40 mL), Na_2CO_3 (20 mL, 2 M) and 3-thienylboronic acid (3.00 g, 23.4 mmol) in MeOH (12 mL) as described above for the preparation of **10**.[45] The crude product was purified by flash chromatography (EtOAc/pentane (1:1)) to give **11** as a white solid (4.35 g, 16.7 mmol, 86%), pure by NMR; R_f 0.18 (EtOAc/pentane (1:1)); mp/decomp. 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.50 (1H, s, pyr-H2), 8.39 (1H, d, *J* 4.8, pyr-H6), 7.56 (1H, dd, *J* 4.8, 3.2, thieno-H5), 7.51 (1H, br s, NH), 7.43 (1H, d, *J* 2.4, thieno-H2), 7.22 (1H, d, *J* 5.2, thieno-H4), 7.18 (1H, d, *J* 4.8, pyr-H5), 1.24 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 176.4 (C=O), 145.2 (pyr-C6), 143.8 (pyr-C2), 135.8 (thieno-C3), 134.7 (pyr-C4), 131.9 (pyr-C3), 127.8 (thieno-C4), 127.4 (thieno-C5), 124.7 (thieno-C2), 123.7 (pyr-C5), 39.7 (CMe_3), 27.4 (C(CH_3)$_3$); NMR assignments are based on HMBC experiments; IR ν_{max}: 3105, 2965, 1668, 1558, 1513, 1475, 1417, 1398, 1303, 1171, 1160, 858, 830, 788, 747, 734, 671, 652 cm^{-1}; MS *m*/*z* (%): 260 (M^+, 21), 176 (16), 131 (7), 85 (6), 57 (100), 41 (16); HRMS calcd for $C_{14}H_{16}N_2OS$: 260.0983; obsd 260.0986. Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.58; H, 6.19; N, 10.76; S, 12.32. Found: C, 64.77; H, 6.30; N, 10.58; S, 12.23.

4.11. 4-(Thien-2-yl)pyridin-3-amine (12)

A solution of amide **10** (1.87 g, 7.19 mmol) in H_2SO_4 (100 mL, 25%, aq) was heated to reflux and kept stirring for 3 h. The reaction was allowed to cool to room temperature before a mixture of NH_3 (150 mL, concd) and ice was added (pH=11). Extraction afforded the yellow/brown crude oily product. Flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) afforded amine **12** as a pale yellow oil (1.24 g, 98%), which soon turned brown: R_f 0.19 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.17 (1H, s, pyr-H2), 8.03 (1H, d, *J* 4.8, pyr-H6), 7.43 (1H, dd, *J* 5.2, 1.2, thieno-H5), 7.35 (1H, dd, *J* 3.6, 1.2, thieno-H3), 7.16 (2H, m, *J* 5.2, 4.8, 3.6, pyr-H5), 4.08 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 140.1 (pyr-C6), 139.5 (pyr-C3), 138.7 (pyr-C2), 138.3 (thieno-C2), 127.9 (thieno-C5), 126.6 (thieno-C4), 126.5 (thieno-C3), 126.2 (pyr-C4), 123.7 (pyr-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 3307, 3169, 1615, 1588, 1550, 1488, 1432, 1418, 1323, 1289, 1237, 1193, 1063, 853, 816, 699 cm^{-1}; MS *m*/*z* (%): 176 (M^+, 100), 131 (57), 77 (16), 51 (9), 39 (6); HRMS calcd for $C_9H_8N_2S$: 176.0408; obsd 176.0407. Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.90. Found: C, 61.31; H, 4.51; N, 15.85.

4.12. 4-(Thien-3-yl)pyridin-3-amine (13)

The title compound was prepared from **11** (4.11 g, 15.8 mmol) in H_2SO_4 (200 mL, 25%, aq) as described above for the preparation of **12**. Extraction afforded a yellow-brown crude oil and flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) gave amine **13** as a transparent oil, which soon turned brown (2.72 g, 98%), pure by NMR; R_f 0.19 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.15 (1H, s, pyr-H2), 8.03 (1H, d, *J* 4.8, pyr-H6), 7.51 (1H, dd, *J* 3.2, 1.2, thieno-H2), 7.46 (1H, dd, *J* 5.2, 3.2, thieno-H5), 7.29 (1H, dd, *J* 5.2, 1.2, thieno-H4), 7.09 (1H, d, *J* 4.8, pyr-H5), 3.94 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 140.1 (pyr-C6), 139.9 (pyr-C3), 138.3 (pyr-C2), 137.2 (thieno-C3), 128.5 (pyr-C4), 127.4 (thieno-C4), 126.8 (thieno-C5), 123.7 (thieno-C2), 123.6 (pyr-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 3311, 3175, 1614, 1591, 1555, 1490, 1423, 1321, 1285, 1233, 1185, 1062, 1039, 842, 825, 788, 750 cm^{-1}; MS *m*/*z* (%): 176 (M^+, 100), 131 (75), 77 (45), 51 (33), 45 (31), 41 (16); HRMS calcd for $C_9H_8N_2S$: 176.0408; obsd 176.0407. Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.90; S, 18.19. Found: C, 61.45; H, 4.58; N, 15.67; S, 18.09.

4.13. 3-Azido-4-(thien-2-yl)pyridine (14)

To a stirred solution of **12** (256 mg, 1.45 mmol) in H_2SO_4 (13 mL) at 0 °C was added $NaNO_2$ (150 mg, 2.18 mmol) in H_2O (10 mL) dropwise during 30 min. The reaction mixture was kept stirring for 20 min at 0 °C before NaN_3 (140 mg, 2.15 mmol) was added dropwise during 40 min at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then kept stirring overnight at room temperature. NaOH (100 mL, 5 M) was added slowly (pH=14). After extraction with CH_2Cl_2, the crude product was purified by flash column chromatography (4% Et_3N in EtOAc/pentane (2:1)). Azide **14** was isolated as a brown oil, crystallising from pentane (212 mg, 72%), pure by NMR. Pyridazine **2a** (40.5 mg, 15%) was also isolated as crystals. Compound **14**: R_f 0.53 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.58 (1H, s, pyr-H2), 8.37 (1H, d, *J* 5.2, pyr-H6), 7.70 (1H, dd, *J* 4.0, 1.2, thieno-H5), 7.50 (2H, d, *J* 5.2, pyr-H5+thieno-H3), 7.16 (1H, dd, *J* 5.2, 4.0, thieno-H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 145.7 (pyr-C2), 141.7 (pyr-C6), 136.1 (thieno-C2), 132.4 (pyr-C4), 132.1 (pyr-C3), 128.6 (2×C, thieno-C4/-C5), 127.6 (thieno-C3), 122.0 (pyr-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 3053, 2127, 2103, 1580, 1544, 1236, 1478, 1413, 1309, 1298, 1259, 1056, 855, 836, 825, 727, 712, 662 cm^{-1}; MS *m*/*z* (%): 202 (M^+, 6), 174 (100), 146 (39), 120 (18), 103 (24), 96 (14), 69 (15), 45 (31), 39 (17), 28 (48); HRMS calcd for $C_9H_6N_4S$: 202.0313; obsd 202.0311.

4.14. 3-Azido-4-(thiophen-3-yl)pyridine (15)

To a stirred solution of azide **17** (434 mg, 2.18 mmol) and Pd(PPh_3)$_4$ (127 mg, 0.110 mmol) in toluene (20 mL) was added Na_2CO_3 (10 mL, 2 M) and 3-thienylboronic acid (337 mg, 2.630 mmol) in MeOH (5 mL).[45] The reaction was heated to 80 °C and kept stirring for 4 h. The reaction mixture was cooled to room temperature, CH_2Cl_2 (40 mL) and NH_3 (2 mL, concd) in Na_2CO_2 (20 mL, 2 M) added and extracted with CH_2Cl_2 (2×20 mL). The brown, oily crude product was purified by flash chromatography (1:2 EtOAc/pentane) to give **15** as a brown oil crystallising from pentane (277 mg, 63%); R_f 0.38 (EtOAc/pentane (1:2)), pure by NMR; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.57 (1H, s, pyr-H2), 8.39 (1H, d, *J* 5.1, pyr-H6), 7.80 (1H, dd, *J* 2.7, 1.5, pyr-H5), 7.45–7.40 (2H, m, thieno-H2/H5), 7.38 (1H, d, *J* 5.1, thieno-H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 146.1, 141.6, 135.3 134.3, 133.3, 127.6, 126.2, 125.9, 123.4; IR (film) ν_{max}: 2124, 2102, 1587, 1420, 1307, 791, 744, 695 cm^{-1}; MS *m*/*z* (%): 202 (M^+, 5), 174 (100), 146 (47), 120 (14), 103 (17), 45 (16); HRMS calcd for $C_9H_6N_4S$: 202.0313; obsd 202.0312. Anal. Calcd for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70. Found: C, 53.39; H, 3.05; N, 27.78.

4.15. 3-Amino-4-bromopyridine (16)[46]

The title compound was prepared from **9** (7.00 g, 27.2 mmol) in H_2SO_4 (120 mL, 20%, aq) as described above for the preparation of **12**. Extraction afforded a yellow crude oil and flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) gave **16** as a colourless oil, which

soon turned brown (3.98 g, 23.0 mmol, 85%), pure by NMR; R_f 0.24 (4% Et_3N in EtOAc/pentane (2:1)); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.09 (1H, s, H2), 7.76 (1H, d, *J* 5.2, H6), 7.31 (1H, d, *J* 5.2, H5); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 141.5 (C3), 139.6/137.4 (C2/C6), 127.4 (C5), 117.9 (C4); IR (film) ν_{max}: 3449, 3315, 3180, 1623, 1574, 1556, 1484, 1417, 1328, 1235, 1058, 811, 669 cm^{-1}; MS *m*/*z* (%): 174 ($C_5H_5^{81}BrN_2$, M^+, 44), 172 ($C_5H_5^{79}BrN_2$, M^+, 47), 147 (12), 145 (12), 93 (47), 66 (100), 39 (38); HRMS calcd for $C_5H_5^{79}BrN_2$: 171.9636; obsd 171.9639.

4.16. 3-Azido-4-bromopyridine (17)

To a stirred solution of $NOBF_4$ in MeCN (15 mL) at −10 °C, amine **16** (2.42 g, 13.99 mmol) in MeCN (5 mL) was added over 15 min. The reaction was allowed to heat to 0 °C and then kept stirring for 30 min. The reaction was cooled to −10 °C and NaN_3 in H_2O (5 mL)/MeCN (2 mL) was added over 30 min. The reaction was kept stirring for 30 min at 0 °C before H_2O (10 mL) was added. Extraction with CH_2Cl_2 afforded an oily crude product. Purification by flash chromatography (1:5 EtOAc/pentane) gave **17** as a light brown oil (1.657, 8.33 mmol, 60%), pure by NMR; R_f 0.25 (1:5 EtOAc/pentane); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.46 (1H, s, C2), 8.19 (1H, d, *J* 5.2, C6), 7.50 (1H, d, *J* 5.2, C5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.1, 141.2, 136.3, 128.3, 123.6; IR (film) ν_{max}: 2113, 1551, 1477, 1405, 1325, 1312, 1066, 824, 703 cm^{-1}; MS *m*/*z* (%): 200 ($C_5H_5^{81}BrN_4$, M^+, 4), 198 ($C_5H_5^{79}BrN_4$, M^+, 4), 172 (28), 170 (25), 91 (32), 64 (100) 37 (27); HRMS calcd for $C_5H_3^{79}BrN_4$: 197.9541; obsd 197.9548.

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Paper II

Vegar Stockmann, Kristine L. Eriksen and Anne Fiksdahl

Preparation of novel pyridine-fused tris-heterocycles; pyrido[4,3-*e*]pyrrolo-/ pyrido[4,3-*e*]furano[2,3-*c*]pyridazines and pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole

Tetrahedron **2008**, *64*, 11180.

Tetrahedron 64 (2008) 11180–11184

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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ARTICLE INFO

Article history:
Received 18 July 2008
Received in revised form 1 September 2008
Accepted 18 September 2008
Available online 26 September 2008

Keywords:
Pyrido[4,3-*e*]pyrrolo[2,3-*c*]pyridazine
Pyrido[4,3-*e*]furano[2,3-*c*]pyridazine,
N-TIPS-pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole
Diazotisation
Diazocoupling
Azide thermal decomposition
4-(3-Furanyl)pyridin-3-amine
4-(3-Pyrrolyl)pyridin-3-amine

ABSTRACT

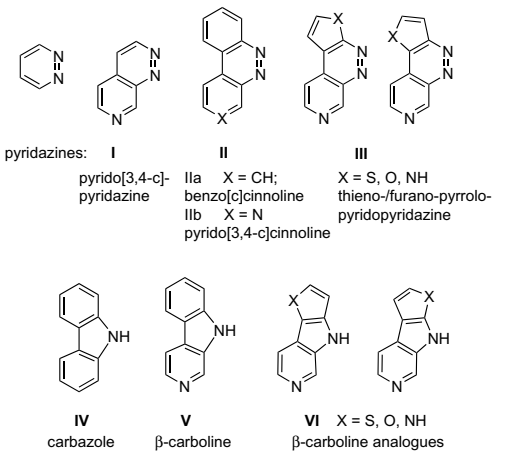
Three novel pyrido-fused tris-heterocycles have been prepared based on a Suzuki coupling and subsequent cyclisation approach. Pyrido[4,3-*e*]pyrrolo[2,3-*c*]pyridazine (**3b**, 77%) and pyrido[4,3-*e*]furano[2,3-*c*]pyridazine (**5b**, 76%) were obtained by intramolecular diazocoupling. Successful diazocoupling of furan (**5b**) is thus reported for the first time by $NOBF_4$ generation of the diazonium intermediate. *N*-TIPS-pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole (**TIPS-4b**) was synthesised by thermal cyclisation of pyridyl nitrene in considerably higher yield (71%) than previously experienced from similar cyclisations, due to TIPS-activation.

1. Introduction

We have previously[1] studied the preparation of two novel groups of thiophene-pyridine-fused tris-heterocycles, pyridazines **III** and β-carboline analogues **VI** (Scheme 1). (i) Pyridazines may, in general, exist as fused heterocycles, such as benzo[*c*]cinnolines (**IIa**), the *N*-analogues pyrido[3,4-*c*]cinnolines (**IIb**) and the pyridopyridazines (**I**). (ii) β-Carbolines (**V**), being *N*-analogues of carbazoles (**IV**), are naturally occurring alkaloids.

Both groups of compounds exhibit diverse biological activities and a number of studies of such effects have been carried out. Their ring structures are incorporated into a series of pharmaceuticals.[1] The phenyl-ring of benzo-fused compounds may be replaced by heterocyclic moieties in order to prepare a series of novel heterocyclic compounds. Such heterocycle-fused analogues may in general offer some advantages from a medicinal chemistry point of view, since the new heteroatom may provide better water solubility by offering an additional site for protonation or salt formation. The heteroatom might also enhance intermolecular interactions by formation of an additional hydrogen bond to target proteins.

Due to the biological activity, the therapeutic use and the generally interesting properties presented above, we are currently investigating the preparation of new closely related heterocyclic analogues of fused pyridazines (**III**) and β-carbolines (**VI**) (Scheme 1). There are, to the best of our knowledge, no reports on products such as **III**, **VI** or similar thieno/pyrrolo/furano compounds except



Scheme 1.

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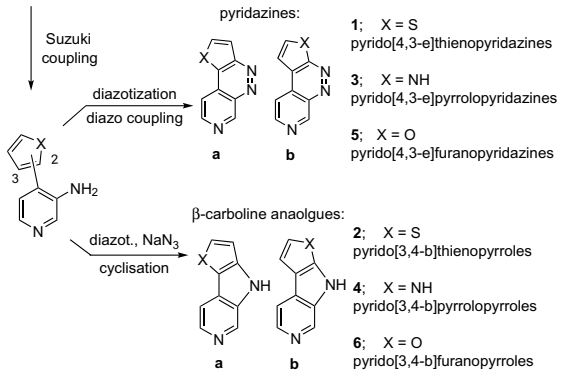
doi:10.1016/j.tet.2008.09.051

for our previous study on the thiophene-heterocycles shown in Scheme 2, the thienopyrido[3,4-*c*]pyridazines (**1a**,**b**) and the thienopyrrolo[2,3-*c*]pyridines (**2a**,**b**).[1] Thieno-compounds **1a**,**b** and **2a**,**b** (**III**, **VI**; X=S) were prepared by a Suzuki–diazotisation approach. Pyrroles and furans are also important heterocycles, being incorporated into many biologically active natural products, such as vitamin B_{12}/porphyrins/bile pigments and furocoumarins/furanterpenoids/ascorbic acid, respectively. Therefore, a subsequent study on the preparation of pyrrole and furan target compounds (**III**, **VI**; X=NH, O) has now been carried out. Our results based on the corresponding strategy, as shown in Scheme 2, are presented below.



Scheme 2.

2. Results and discussion

2.1. Target compounds

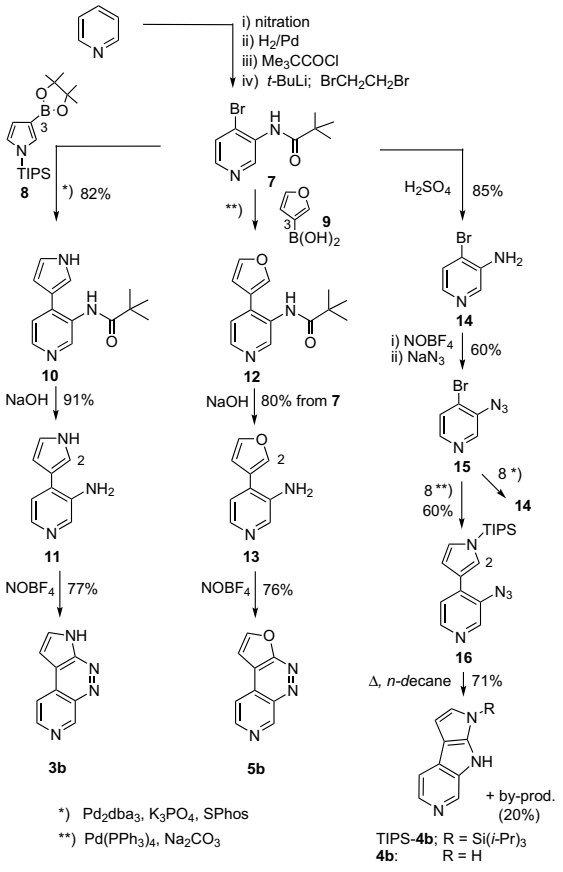
Based on our results with the former preparation[1] of the thieno-heterocycles **1a**,**b** and **2a**,**b**, some observations were made.

All the **b** products shown in Scheme 2, would be formed by ring closure involving the highly reactive 2-position of the thiophene/pyrrole/furan rings. We have previously demonstrated for the thiophene products that lower yields were obtained of **1a**/**2a** compared to **1b**/**2b**, due to the lower reactivity of the 3-position of the thiophene ring. The strongly acidic conditions required for the cyclisation to give thieno product **1a**,[1] would not be suitable for the preparation of **3a** and **5a**, since furans and pyrroles are unstable by such conditions. Consequently, the synthetic strategy presented in Scheme 2 is less appropriate for regioisomers **3a**–**6a**, as these products would be expected to be formed in lower yields than the corresponding **3b**–**6b**. Therefore, the present work was aimed at the pyrrole and furan **b** products (**3b**–**6b**).

The Suzuki–nitrene approach includes a thermal decomposition of an arylazide for the final pyrrole cyclisation by nitrene CH insertion. The method has been used with success for the preparation of carbazoles (**IV**, Scheme 1). However, only low yields (15–30%) of β-carboline **V**,[2] and thieno-analogues **VI** (X=S) have been obtained by thermal decomposition of the respective pyridyl azide precursors, as discussed elsewhere for **2a**,**b** (Scheme 2).[1] This may be caused by the electron-deficient character of the pyridine moiety. The method would, therefore, be expected to be less successful for pyrrolo and furano β-carboline analogues **4**,**6** as well. Thus, the present work mainly focussed on (i) the new pyridazine products **3**,**5**. However, the preparation of (ii) pyrrolo-β-carboline analogue **VI** (X=NH) has been studied in the present work (**4b**), and an activation strategy was investigated to examine whether an *N*-triisopropylsilyl (TIPS) group attached to the pyrrole would compensate for the electron-deficient character of the pyridine ring. Consequently, the target compounds for this study were **3b**, **4b** and **5b**.

2.2. Pyridazines

The synthetic pathways for all the target products were based on the Suzuki coupling for the preparation of the essential pyrrolo/furano-pyridine intermediates, as shown in Scheme 3. In Suzuki coupling reactions, (i) electron-deficient aryl halides and (ii) electron-rich boronic acids are the substrates of choice, since those compounds are more reactive than the contrary in, respectively, (i) the oxidative addition and (ii) the transmetallation steps. The diaryl-coupling products **10** and **12**, key intermediates in order to prepare the pyridazine products **3b** and **5b**, were therefore prepared from 4-bromopyridine **7**[1] and the pyrrolo/furano boronic reactants **8** and **9**.



Scheme 3.

The appropriate 3-pyrrolylboronate reagent **8** can be made by borylation. In general, C-substitution of pyrrole most readily takes place at the 2-position and direct borylation would exclusively produce 2-borylated products. However, selective borylation at the 3-position of pyrrole has been reported,[5,6] providing a valuable precursor for Suzuki cross-coupling reactions. Coupling at C–H bonds located *ortho* to bulky substituents is slow due to steric hindrance. This effect allows a regioselective synthesis of

3-borylpyrrole, since 3-substitution becomes favoured using *N*-substituted substrates. Sterically hindered *N*-triisopropylsilyl (TIPS) derivatives provide 3-boryl isomers selectively. The TIPS group can eventually be removed by treatment with TBAF or TFA to afford isomerically pure 3-borylpyrrole.[5,6]

N-TIPS-pyrrole was quantitatively obtained from pyrrole and TIPS-Cl without further purification. Regioselective C–H coupling of TIPS-pyrrole with bis(pinacolato)diboron (pin_2B_2) was carried out in octane at 80 °C in the presence of 1/2[IrCl(COD)]-dtbpy catalyst (3 mol %) and afforded the 3-borylated pyrrole reagent **8** (77%).

The pyrrole–pyridine coupling product **10** was prepared (82%) by Suzuki coupling of bromide **7** and the *N*-TIPS-pinacolatopyrroloboronate ester **8**, using $K_3PO_4 \cdot 3H_2O$ and the Pd_2dba_3–SPhos catalytic system (SPhos: 2-dicyclohexylphosphino-2′,6′-dimethoxyphenyl).[3] An additional desilylation step was not required, as the *N*-TIPS group was cleaved in the coupling reaction to give the deprotected pyrrole product **10**. The coupling reaction was, however, not successful using the PEPPSI-IPr precatalyst protocol based on the diisopropylphenylimidazoliumpyridine *N*-heterocyclic carbene system.[4] Several advantages have been reported using Pd_2dba_3–SPhos catalysis for pyridines and pyrroles. Additionally, pyrrolylboronate esters are preferred compared to boronic acid in such Suzuki coupling reactions.[3]

Suzuki coupling of 4-bromopyridine **7** and furylboronic acid **9** afforded nearly quantitative yield of the furylpyridine coupling product **12**.

Alkaline hydrolysis was chosen for the conversion of pivalamides **10** and **12** to the unprotected aminopyridines **11** (91%) and **13** (80% from **7**). As expected, acidic conditions (25% H_2SO_4), previously used[1] for the hydrolysis of corresponding thiophene compounds, were not successful. A number of unidentified products were obtained by acidic hydrolysis of **10**, and only 36% of product **13** was afforded from amide **12**. It is well known that protonation of pyrroles and furans takes place in acidic media and often leads to hydrolysis, cleavage or rapid polymerisation/oligomerisation of the cations.[7]

The intramolecular diazocoupling to generate **3b** and **5b** is highly favoured, as electrophilic substitution at the most reactive 2-position of pyrrole is involved. Due to the instability of furan and pyrrole in acidic media, traditional $NaNO_2/H_2SO_4$ also had to be avoided for the diazotisation of amines **11** and **13**. Exclusive formation of pyrrolopyridazine **3b** (77%) and furanopyridazine **5b** (76%) was obtained by intramolecular diazocoupling of the diazonium intermediate generated by $NOBF_4$ from aminopyridines **11** and **13**, respectively.

To the best of our knowledge, this is the first reported successful diazocoupling of furans. Furan is less electron-rich and hence less reactive than pyrroles towards electrophiles. Conventional electrophilic substitution may, in general, be difficult to achieve for furans. While pyrroles readily undergo diazocoupling, azo-coupling reactions have been reported to fail with furan, due to its lower reactivity compared with pyrrole. Furanophenyl azo compounds have, therefore, been made by oxidation of 2-furanone hydrazones,[8] or by *ipso* arene diazonium substitution of 2-substituted furans.[9] Only the activated benzo-fused 3-(acetylamino)-5-methoxybenzofuran has been reported to undergo azo-coupling.[10]

The dipole moment of pyrrole is directed from nitrogen to carbon, opposite to furan and thiophene. Due to the higher electron density of pyrrole compared with thiophene, expected lower pyrrole NMR shift values ($\Delta\delta_C$ 10–20 ppm and $\Delta\delta_H$ 0.5–0.7 ppm) were observed for all the pyrrole products (**10**,**11** and **3b**) compared to corresponding thiophene compounds previously prepared.[1]

2.3. β-Carboline analogue

In the synthesis of β-carboline analogue **TIPS-4b**, the azide functionality was introduced before the Suzuki cross-coupling. A possible direct preparation of azide **16** from amino precursor **11** by diazotisation and azide substitution[1] would only give the azo-coupling pyridazine product **3b**, due to the highly reactive pyrrole 2-position. However, the reaction of pinacolatopyrroloboronate ester **8** and 3-azido-4-bromopyridine **15**,[1] using $K_3PO_4 \cdot 3H_2O$ and the Pd_2dba_3–SPhos catalytic system described above, was unsuccessful for the preparation of coupling product **16**. Reduction of the azide group took place and only the 3-aminopyridine compound **14** was isolated. On the other hand, the coupling product **16** was readily formed (60%) by $Pd(PPh_3)_4$ catalysis, using Na_2CO_3 as a base. In contrast to the formation of **10** above, the *N*-TIPS group was not cleaved.

The cyclisation by thermal decomposition of azidopyridine **16** via the nitrene afforded **TIPS-4b** in 71% yield. The significantly higher yield obtained for **TIPS-4b** relative to the previously reported β-carboline[2] and thieno[1] products (15–30%), indicates that the *N*-TIPS group in substrate **16** offers an activating effect, which may compensate for the electron-deficient character of the pyridine ring. Small amounts of the TIPS group were cleaved in the cyclisation step in some of the experiments to afford approximately 10% of the unprotected product **4b**. Preparative desilylation of **TIPS-4b** was carried out by TBAF[5,6] cleavage. Full conversion into the deprotected product **4b** was directly obtained, as shown by NMR spectroscopy.

The thermal decomposition of azide **16** also afforded an additional by-product (20%). This new compound was similar to a by-product previously isolated from the formation of the corresponding thieno product **2b** (Scheme 2). The nature of these compounds is being investigated.[11]

3. Conclusion

Three novel pyrido-fused tris-heterocycles have been prepared by Suzuki coupling and subsequent cyclisations. Pyrido[4,3-*e*]pyrrolo[2,3-*c*]pyridazine (**4b**, 77%) and pyrido[4,3-*e*]furano[2,3-*c*]pyridazine (**5b**, 76%) were obtained by intramolecular diazocoupling. Successful diazocoupling of furans (**5b**) is thus reported for the first time by $NOBF_4$ generation of the diazonium intermediate. Due to activation by an *N*-TIPS group, thermal cyclisation of pyridyl nitrene afforded the β-carboline analogues *N*-TIPS-pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole (**TIPS-4b**) in considerably higher yield (71%) than previously experienced from similar cyclisations.[1,2]

4. Experimental

4.1. General

Chemicals: Pyrrole, TIPS-Cl, *n*-BuLi, pin_2B_2, 2-(4,4′-di-*tert*-butyl-2,2′-bipyridine) (dtbpy), [IrCl(COD)], Pd_2dba_3, SPhos, 3-furanboronic acid (Sigma–Aldrich); $NOBF_4$, $Pd(PPh_3)_4$ (Fluka); $K_3PO_4 \cdot 3H_2O$ (Merck). Solvents: pro analysi quality. $^1H/^{13}C$ NMR: Bruker Avance DPX 300 and 400 spectrometers, chemical shifts are reported in parts per million downfield from TMS. *J* values are given in hertz. EIMS: Finnigan MAT 95 XL (70 eV). ESI-MS accurate mass determinations were performed on an Agilent 6520 QTOF MS instrument equipped with a dual electrospray ion source for continuous injection of mass axis calibrants through the second nebuliser needle. Samples were injected into the MS using an Agilent 1200 series HPLC and analysis was performed as a flow injection analysis without any chromatographic step. IR: Nicolet 20SXC FT-IR spectrophotometer. All melting points are uncorrected, measured on a Stuart apparatus. Elemental analyses were done by the Laborator Beller/Matties, Göttingen, Germany. Flash chromatography: Silica (SDS, 60 Å, 40–63 μm). Organic solvent extracts were dried with anhydrous sodium sulfate. Compounds **7**, **14** and **15** were prepared according to the literature.[1] Compounds

3b, **TIPS-4b**, **5b** and **12** were synthesised by methods similar to previously described procedures for preparation of the corresponding thiophene compounds.[1] All reactions were conducted under nitrogen atmosphere unless otherwise noted.

4.2. Pyrido[4,3-*e*]pyrrolo[2,3-*c*]pyridazine (3b)

The title compound was prepared by diazocoupling[1] from amine **11** (58.0 mg, 0.64 mmol) in dry MeCN (7 mL) and $NOBF_4$ (110 mg, 0.942 mmol) in dry MeCN (5 mL). Product **3b** was obtained as an off-white solid (47.0 mg, 77%) after flash chromatography on a Al_2O_3 column (gradient; 0–5% MeOH in CH_2Cl_2), pure by NMR. R_f 0.38 (5% MeOH in CH_2Cl_2, Al_2O_3-TLC); mp >232 °C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ_H 13.36 (1H, br, NH), 9.81 (1H, s, py-H2), 8.77 (1H, d, *J* 6.0, py-H6), 8.32 (1H, d, *J* 6.0, py-H5), 8.09 (1H, t, *J* 2.8, pyrrole-H5), 7.32 (1H, dd, *J* 2.8, 1.6, pyrrole-H4); ^{13}C NMR (100 MHz, DMSO): δ_C 154.1 (py-C2), 148.9 (pyrrole-C2), 145.8 (py-C6), 139.9 (py-C3), 130.9 (pyrrole-C5), 124.8 (py-C4), 116.6 (py-C5), 112.5 (pyrrole-C3), 100.4 (pyrrole-C4); NMR assignments are based on HSQC and HMBC experiments; IR (KBr) ν_{max} 3265br, 3069m, 3010m, 1651s, 1434m, 1245m, 1113s, 813s, 767s cm^{-1}; MS *m*/*z* (%) 170 (M^+, 100), 115 (84), 88 (20); EI-HRMS calcd for $C_9H_6N_4$: 170.0593; obsd: 170.0587.

4.3. Pyrido[3,4-*b*]-(1-triisopropylsilyl-1*H*-pyrrolo)[3,2-*d*]pyrrole (TIPS-4b)

The title compound was prepared by thermal decomposition[1] of azide **16** (107 mg, 0.313 mmol) in dry *n*-decane (60 mL). The reaction mixture was heated to reflux and kept stirring for 40 min, cooled to room temperature and decane was distilled off. Flash chromatography (gradient; 1–10% MeOH/CH_2Cl_2) afforded **TIPS-4b** as an off-white solid (70 mg, 71%), pure by NMR. R_f 0.11 (10% MeOH in CH_2Cl_2); mp >95 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.71 (1H, s, py-H2), 8.26 (1H, d, *J* 5.6, py-H6), 7.57 (1H, d, *J* 5.6, py-H5), 6.76 (1H, d, *J* 3.2, pyrrole-H5), 6.64 (1H, d, *J* 3.2, pyrrole-H4), 1.63 (3H, sep, *J* 7.6, C*H*(CH_3)$_2$), 1.18 (18H, d, *J* 7.6, CH(C*H*$_3$)$_2$); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.91 (1H, br s, NH), 8.63 (1H, s, py-H2), 8.09 (1H, d, *J* 5.6, py-H6), 7.51 (1H, d, *J* 5.6, py-H5), 6.83 (1H, d, *J* 3.2, pyrrole-H5), 6.58 (1H, d, *J* 3.2, pyrrole-H4), 1.76 (3H, sep, *J* 7.6, C*H*(CH_3)$_2$), 1.10 (18H, d, *J* 7.6, CH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 146.5 (pyrrole-C2), 137.7 (py-C6), 137.5 (py-C3), 132.4 (py-C2), 126.7 (py-C4), 125.1 (pyrrole-C5), 113.2 (py-C5), 109.9 (pyrrole-C3), 102.4 (pyrrole-C4), 18.0 (TIPS-*C*H$_3$), 12.2 (TIPS-*C*H); NMR assignments are based on HMBC experiments; IR (KBr) ν_{max} 3379w br, 3105m br, 3067m, 2947s, 2867s, 1609m, 1524m, 1095s, 883m, 707s cm^{-1}; ESI-HRMS: calcd for $[M+H]^+$ $C_{18}H_{28}N_3Si$: 314.2047; obsd: 314.2050.

4.4. Pyrido[3,4-*b*]-(pyrrolo)[3,2-*d*]pyrrole (4b)

To an NMR sample of **TIPS-4b** (approx. 4 mg in 1 mL $CDCl_3$) was added TBAF (excess). Quantitative conversion to **4b** took place within an hour, as shown by ^{1}H NMR spectroscopy. 1,2,4,5-Tetrachlorobenzene was used as internal standard. Compound **4b**: R_f 0.15 (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.75 (1H, s, py-H2), 8.12 (1H, d, *J* 5.6, py-H6), 7.44 (1H, d, *J* 5.6, py-H5), 6.81 (1H, d, *J* 3.2, pyrrole-H5), 6.35 (1H, d, *J* 3.2, pyrrole-H4); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.26 (2H, br s, 2×NH), 8.55 (1H, s, py-H2), 8.04 (1H, d, *J* 5.2, py-H6), 7.45 (1H, d, *J* 5.2, py-H5), 6.75 (1H, d, *J* 3.2, pyrrole-H5), 6.35 (1H, d, *J* 3.2, pyrrole-H4); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 142.7 (pyrrole-C2), 137.7 (py-C6), 137.1 (py-C3), 132.5 (py-C2), 127.1 (py-C4), 119.1 (pyrrole-C5), 113.2 (py-C5), 107.1 (pyrrole-C3), 99.7 (pyrrole-C4); NMR assignments are based on HSQC and HMBC experiments; ESI-HRMS calcd for $[M+H]^+$ $C_9H_8N_3$: 158.0713; obsd: 158.0712.

4.5. Pyrido[4,3-*e*]furano[2,3-*c*]pyridazine (5b)

The title compound was prepared by diazocoupling[1] from amine **13** (32.4 mg, 0.202 mmol) in dry MeCN (5 ml) and $NOBF_4$ (117 mg, 1.00 mmol) in dry MeCN (5 mL). Purification by flash chromatography (10% MeOH/CH_2Cl_2) afforded pyridazine **5b** (26.3 mg, 76%) as a white solid, pure by NMR. R_f 0.45 (10% MeOH/CH_2Cl_2); mp >200 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 10.09 (1H, d, *J* 0.9, py-H2), 8.87 (1H, d, *J* 6.0, py-H6), 8.17 (1H, d, *J* 2.4, furan-H5), 7.99 (1H, dd, *J* 6.0, 0.9, py-H5), 7.40 (1H, d, *J* 2.4, furan-H4); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 162.9 (furan-C2), 156.3 (py-C2), 148.8 (furan-C5), 147.2 (py-C6), 143.0 (py-C3), 126.1 (py-C4), 116.2 (py-C5), 115.3 (furan-C3), 105.4 (furan-C4); NMR assignments are based on HMBC experiments; IR (KBr) ν_{max} 3098w, 1619s, 1502s, 1401m, 1225m, 1113m, 1048m, 869m, 844m, 776s cm^{-1}; MS *m*/*z* (%)171 (M^+, 17%), 170 (100), 114 (40), 88 (47); EI-HRMS calcd for $C_9H_5N_3O$: 171.0433; obsd: 171.0436. Anal. Calcd for $C_9H_5N_3O$: C, 63.16; H, 2.94; N, 24.55. Found: C, 62.72; H, 2.54; N, 24.23.

4.6. 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (8)[5,6]

The title compound was prepared according to the literature[5,6] from pyrrole via TIPS-pyrrole (1-(triisopropylsilyl)-1*H*-pyrrole);

(i) pyrrole (1.94 mL, 28 mmol), dry THF (45 mL), *n*-BuLi (18.1 mL, 30.8 mmol) and TIPS-Cl (5.7 mL, 26.9 mmol) afforded TIPS-pyrrole as a yellow oil (5.99 g, 99%) after extraction, pure by NMR;[12] R_f 0.95 (EtOAc/pentane 2:1), used without further purification;

(ii) pin_2B_2 (1.24 g, 4.88 mmol), $[IrCl(COD)]_2$ (69.5 mg, 0.103 mmol), dtbpy (58.8 mg, 0.219 mmol) and TIPS-pyrrole (6.41 g, 28.7 mmol) in octane (20 mL), gave a black crude product after stirring for 48 h at 80 °C and subsequent evaporation of the solvent. Excess TIPS-pyrrole was removed by distillation (4–6 mbar, approx. 80 °C) and flash chromatography of the residue (EtOAc/pentane 1:5) afforded product **8** as a white solid (2.61 g, 77% from pin_2B_2), pure by NMR. R_f 0.85 (EtOAc/pentane 1:5); mp 70–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.23 (1H, dd, *J* 1.4, 2.6), 6.81 (1H, dd, *J* 2.6, 2.1), 6.62 (1H, dd, *J* 2.6, 1.4), 1.46 (3H, sep, *J* 7.4), 1.32 (12H, s), 1.09 (18H, d, *J* 7.4).

4.7. *N*-[4-(1*H*-Pyrrol-3-yl)pyridin-3-yl]pivalamide (10)

A solution of **7** (1.04 g, 4.04 mmol), pyrrole **8** (1.70 g, 4.87 mmol), $K_3PO_4 \cdot 3H_2O$ (2.16 g, 8.11 mmol), Pd_2dba_3 (109 mg, 0.119 mmol), SPhos (97 mg, 0.236 mmol) in *n*-butanol (30 mL) and distilled water (12 mL) was heated to 100 °C, stirred overnight and cooled to room temperature.[3] The solution was concentrated and water (20 mL) was added. After extraction with ether (3×20 mL), evaporation of the solvent and flash chromatography (gradient; 1–5% MeOH/CH_2Cl_2) product **10** was obtained as a white solid (804 mg, 82%), pure by NMR spectroscopy. R_f 0.20 (5% MeOH/CH_2Cl_2); mp >135 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.54 (s, 1H, py-H2), 9.05 (br s, 1H, NH), 8.32 (d, 1H, *J* 5.2, py-H6), 7.92 (1H, br s, NH), 7.22 (d, 1H, *J* 5.2, py-H5), 6.99 (m, 2H, pyrrole-H2/H5), 6.39 (dd, 1H, *J* 4.2, 2.8, pyrrole-H4), 1.27 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 176.7 (C=O), 145.1 (py-C6), 143.2 (py-C2), 134.4 (py-C4), 132.3 (py-C3), 123.9 (py-C5), 120.1 (pyrrole-C2), 118.6 (pyrrole-C3), 117.6 (pyrrole-C5), 108.5 (pyrrole-C4), 40.0 (*C*Me$_3$), 27.8 (C(*C*H$_3$)$_3$); NMR assignments are based on HSQC and HMBC experiments; IR (KBr) ν_{max} 3318s br, 2966w, 1653s, 1419m, 1307s, 1034m, 789m cm^{-1}; MS *m*/*z* (%) 243 (M^+, 51), 159 (35), 131 (18), 104 (8); EI-HRMS calcd for $C_{14}H_{17}N_3O$: 243.1373; obsd: 243.1372.

4.8. 4-(1*H*-3-Pyrrolyl)pyridin-3-amine (11)

Pivalamide **10** (475 mg, 1.95 mmol) was dissolved in NaOH (8 M, 50 mL) and ethanol (50 mL) and heated at reflux for 26 h. The mixture was cooled to room temperature and the solvent was evaporated. Water (50 mL) was added and the product was extracted into CH_2Cl_2 (5×30 mL). Product **11** was obtained as a slightly yellow solid (283 mg, 91%), pure by NMR, after flash chromatography (5% MeOH in CH_2Cl_2). R_f 0.11 (5% MeOH in CH_2Cl_2); mp 132–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.08 (1H, br s, NH), 8.10 (1H, s, py-H2), 8.00 (1H, d, *J* 4.2, py-H6), 7.16 (2H, m, py-H5/pyrrole-H5), 6.92 (1H, dd, *J* 4.4, 2.7, pyrrole-H2), 6.52 (1H, dd, *J* 4.4, 2.7, pyrrole-H4), 3.93 (2H, br, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 140.3 (py-C6), 139.7 (py-C3), 138.0 (py-C2), 129.1 (py-C4), 123.0 (py-C5), 119.7 (pyrrole-C3), 119.2 (pyrrole-C2), 117.0 (pyrrole-C5), 108.1 (pyrrole-C4); NMR assignments are based on HSQC and HMBC experiments; IR (KBr) ν_{max} 3389m, 3322w, 3159w, 1586s, 1324s, 1085s, 1037s, 671s cm^{-1}; MS *m*/*z* 159 (M^+, 80%), 158 (44), 132 (21), 104, (18); EI-HRMS calcd for $C_9H_9N_3$: 159.0797; obsd: 159.0791.

4.9. *N*-(4-(Furan-3-yl)pyridin-3-yl)pivalamide (12)

The title compound was prepared by Suzuki coupling[1] from **7** (1.07, 4.16 mmol) and **9** (557 mg, 4.98 mmol) affording 1.10 g of a solid (containing small amounts of aromatic impurities, as shown by NMR spectroscopy) after flash chromatography (4% Et_3N in EtOAc/pentane (2:1)). This crude product was used directly in the next step for the preparation of **13** below. A pure sample prepared for analysis had R_f 0.30 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.36 (1H, s, py-H2), 8.36 (1H, d, *J* 5.1, py-H6), 7.67 (1H, dd, *J* 1.4, 0.9, furan-H2), 7.62 (1H, dd, *J* 1.8, 1.4, furan-H5), 7.49 (1H, br s, NH), 7.20 (1H, d, *J* 5.1, py-H5), 6.59 (1H, dd, *J* 1.8, 0.9, furan-H4), 1.24 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 176.7 (C=O), 145.7 (py-C6), 144.7 (furan-C5), 144.5 (py-C2), 141.1 (furan-C2), 132.1 (py-C3), 131.5 (py-C4), 123.7 (py-C5), 120.8 (furan-C3), 110.4 (furan-C4), 40.0 (*C*Me$_3$), 27.7 (C(*CH*$_3$)$_3$); NMR assignments are based on HSQC and HMBC experiments; IR (film) ν_{max} 3287s br, 2967s, 1660s, 1602m, 1503s, 1414m, 1301m, 1161s, 1059w, 1017m, 874s, 796m cm^{-1}; MS *m*/*z* (%) 244 (M^+, 44), 160 (10), 131 (21), 91 (100); EI-HRMS calcd for $C_{14}H_{16}N_2O_2$: 244.1209; obsd: 244.1212.

4.10. 4-(Furan-3-yl)pyridin-3-amine (13)

The crude product (1.10 g) obtained from the preparation of **12** above, was dissolved in NaOH (50 mL, 8 M) and EtOH (60 mL, 96%). The solution was heated to reflux and kept stirring for 70 h. The reaction was allowed to cool to room temperature and concentrated under reduced pressure. Water (100 mL) and CH_2Cl_2 (50 mL) were added, the aqueous phase was extracted with CH_2Cl_2 (3×30 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated. The brown, oily crude product was purified by flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) to give amine **13** (533 mg, 80% from **7**) as a white solid, pure by NMR spectroscopy. R_f 0.24 (4% Et_3N in EtOAc/pentane (2:1)); mp 70–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.16 (1H, s, py-H2), 8.04 (1H, d, *J* 5.0, py-H6), 7.79 (1H, dd, *J* 1.6, 1.0, furan-H2), 7.56 (1H, dd, *J* 2.0, 1.6, furan-H5), 7.10 (1H, d, *J* 5.0, py-H5), 6.69 (1H, dd, *J* 2.0, 1.0, furan-H4), 3.85 (2H, br s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 144.0 (furan-C5), 140.8 (furan-C2), 140.5 (py-C6), 140.1 (py-C3), 138.6 (py-C2), 125.3 (py-C4), 123.1 (py-C5), 121.8 (furan-C3), 110.1 (furan-C4); NMR assignments are based on HSQC and HMBC experiments; IR (KBr) ν_{max} 3321s br, 3182s br, 1625m, 1423s, 1322m, 1161s, 1055w, 1017m, 874s cm^{-1}; MS *m*/*z* (%) 160 (M^+, 100%), 131 (99), 103 (13), 76 (11); EI-HRMS calcd for $C_9H_8N_2O$: 160.0637; obsd: 160.0638. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.09; H, 5.06; N, 16.81.

4.11. 3-Azido-4-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)-pyridine (16)

The title compound was prepared by Suzuki coupling from azide **5** (290 mg, 1.46 mmol), $Pd(PPh_3)_4$ (84.0 mg, 5.0 mol %) in toluene (20 mL), Na_2CO_3 (10 mL, 2 M) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (**8**) (610 mg, 1.75 mol) in MeOH (5 mL). The crude product was purified by flash chromatography (gradient; 0–5% CH_2Cl_2 in MeOH), to give product **16** as a brown oil (299 mg, 60%), pure by NMR. R_f 0.31 (2% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.47 (1H, s, py-H2), 8.28 (1H, d, *J* 5.4, py-H6), 7.51 (1H, dd, *J* 2.0, 1.6, pyrrole-H2), 7.41 (1H, d, *J* 5.4, py-H5), 6.82 (1H, dd, *J* 3.2, 2.0, pyrrole-H5), 6.74 (1H, dd, *J* 3.2, 1.6, pyrrole-H4), 1.48 (3H, sep, *J* 7.4, TIPS-C*H*), 1.13 (18H, d, *J* 7.4, TIPS-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 146.0 (py-C6), 141.5 (py-C2), 134.7 (py-C4), 132.2 (py-C3), 126.3 (pyrrole-C2), 125.1 (pyrrole-C5), 121.8 (py-C5), 120.2 (pyrrole-C3), 110.2 (pyrrole-C4), 17.9 (TIPS-*C*H$_3$), 11.8 (TIPS-*C*H); NMR assignments are based on HSQC and HMBC experiments; IR (film) ν_{max} 2946m, 2868m, 2108s, 1589s, 1308s, 1119s, 884s, 803s, 703s, 662s cm^{-1}; MS *m*/*z* (%) 341 (M^+, 8), 313 (94), 271 (68), 270 (100), 242 (23), 228 (95), 200 (65), 186 (63), 185 (18), 157 (15), 129 (10), 115 (33), 107 (13); ESI-HRMS calcd for $[M+H]^+$ $C_{18}H_{28}N_5Si$: 342.2108; obsd: 342.2104.

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Paper III

Vegar Stockmann, Jan M. Bakke, Per Bruheim and Anne Fiksdahl

Formation of new 4-isocyanobut-2-enenitriles by thermal ring cleavage of 3-pyridyl azides

Tetrahedron **2009**, *65*, 3668.

Tetrahedron 65 (2009) 3668–3672

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Formation of new 4-isocyanobut-2-enenitriles by thermal ring cleavage of 3-pyridyl azides

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ARTICLE INFO

Article history:
Received 21 November 2008
Received in revised form 9 February 2009
Accepted 26 February 2009
Available online 5 March 2009

Keywords:
3-Pyridylazide
3-Pyridyl nitrene
Thermolysis
4-Isocyano-2-(thiophen-3-yl)but-2-enenitrile
4-Isocyano-2-(1-TIPS-1*H*-pyrrol-3-yl)but-2-enenitrile
2-(Thien-3-yl)-1*H*-pyrrole-3-carbonitrile

ABSTRACT

A new thermal ring cleavage of 3-pyridyl nitrenes for the formation of 4-isocyanobut-2-enenitrile products is reported. Thermolysis of 4-(thien-3-yl)-3-pyridyl azide **1** and 3-azido-4-(1-TIPS-1*H*-pyrrol-3-yl)pyridine **5** afforded two new isonitrile–nitrile products by ring cleavage; 4-isocyano-2-(thiophen-3-yl)but-2-enenitrile (**3**, 27%) and 4-isocyano-2-(1-TIPS-1*H*-pyrrol-3-yl)but-2-enenitrile (**7**, 20%), in addition to our previously reported pyrido[3,4-*b*]thienopyrrole (**2**, 29%) and pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole (**6**, 71%) products. Minor amounts of 2-(thien-3-yl)-1*H*-pyrrole-3-carbonitrile (**4**, 6%), formed by ring contraction, were also isolated after thermolysis of azide **1**. Isonitriles **3** and **7** underwent degradation into amine **3b** and formamide **7a** by acidic hydrolysis. The nature and chemistry of compounds **3**, **4** and **7** were investigated.

1. Introduction

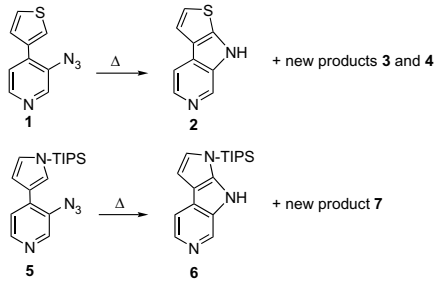
We have previously reported the preparation of new β-carboline thieno and pyrrole analogues (**2**, **6**) by thermal decomposition of 4-(thien-3-yl)-3-pyridyl azide (**1**) and 4-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)pyridyl azide (**5**), respectively (Scheme 1).[1–4]

The thermolysis of 3-pyridyl azides **1** and **5** also afforded additional products (**3**,**4** and **7**). In the present work we have identified these unknown products and studied the transformation reactions into the new compounds. Our results of the investigation of the properties of products **3**, **4** and **7**, in particular by NMR and IR spectroscopy, are discussed below.

2. Results and discussion

2.1. Synthesis

The preparation of the 3-pyridyl azides **1** and **5** was mainly based on pyridine nitration, directed metallation and a Suzuki cross-coupling strategy (Scheme 2).[1] 3-Pyridylpivaloyl amide (**9**) was obtained by nitration of pyridine,[5,6] followed by reduction of the nitro group (91%) and derivatisation with pivaloyl chloride (96%). 4-Bromo-3-amidopyridine (**10**) was prepared (55%) by regioselective electrophilic substitution of **9** by *ortho*-lithiation and reaction with ethylene dibromide. Hydrolysis of intermediate **10** (85%) and subsequent $NOBF_4$ diazotisation/azide substitution (60%) afforded 3-azido-4-bromopyridine **12**. Suzuki couplings of 4-bromopyridine **12** with 3-thienylboronic acid and *N*-TIPS-pinacolatopyrroloboronate ester, respectively, yielded the coupling products **1** (63%) and **5** (60%).



Scheme 1. Cyclisation to β-carboline analogues.

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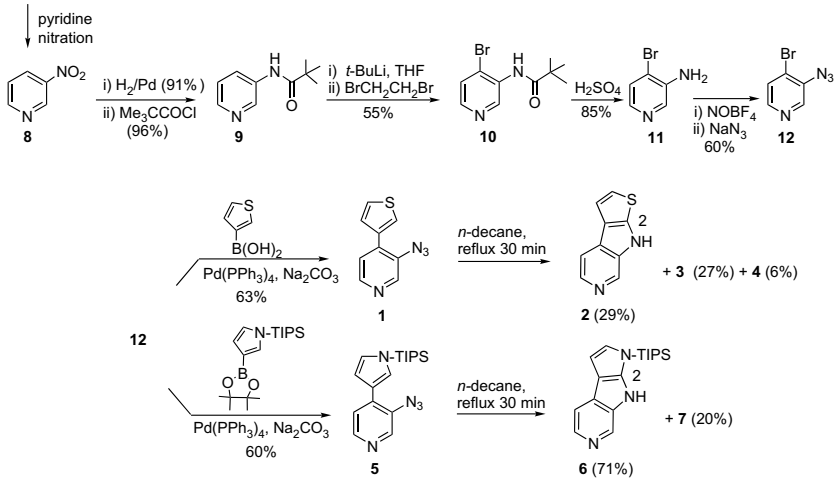
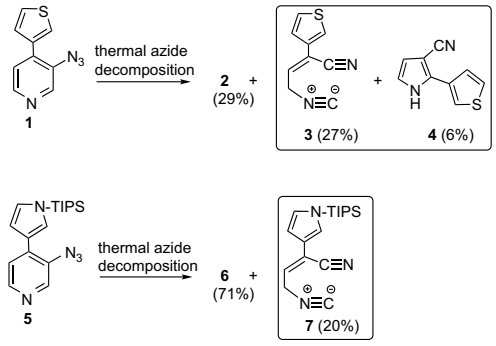
doi:10.1016/j.tet.2009.02.072



Scheme 2.

Cyclisation by thermal decomposition of azides **1** and **5** via the nitrenes, afforded the desired β-carboline analogues **2** (29%) and **6** (71%) by C–H insertion into the 2-thienyl/2-pyrrole positions (Scheme 1). The thermal decomposition of azides **1** and **5** also afforded two considerably less polar new compounds **3** (27%) and **7** (20%), isolated by chromatography after direct evaporation of the solvent (Scheme 3). Minor amounts of an additional product **4** (6%) were isolated from the cyclisation of the thienyl substrate **1**.



Scheme 3.

2.2. Compound 3

Product **3** was stable towards flash chromatography and handling. However, slow degradation was observed after storage in solution at room temperature for several weeks. The structure elucidation of product **3** was mainly based on the spectroscopic and chemical characteristics discussed below in (i)–(vi). In general, all NMR, IR and MS data, including results obtained by a thorough 2D NMR correlation experiments, ATP, NOESY, HSQC and HMBC (Table 1), supported the assumption that a ring cleavage to an isonitrile–nitrile structure, 4-isocyano-2-thiophenylbutenenitrile **3**, had taken place (Scheme 3).

(i) The IR spectrum of compound **3** points towards an isonitrile–nitrile structure. The characteristic absorptions caused by both nitrile and isonitrile stretching vibrations were observed at, respectively, 2231 cm^{-1} (w) and 2154 cm^{-1} (s). Characteristic nitrile MS-fragmentation of HCN (M−27) was observed for product **3**.

(ii) One remarkable structure element of product **3** was, based on ^{1}H NMR spectroscopy, an allylic methylene group, as shown by the characteristic =CH–C$\underline{H}_2$ doublet (δ 4.51, J 6.9 Hz) and the =C$\underline{H}$–CH$_2$ triplet (δ 6.64, J 6.9 Hz) signals. The large coupling constant shows that the allylic element is not part of a planar cyclic system. All the typical pyridyl proton signals from substrate **1** and product **2** were absent.

(iii) The most striking feature was, however, the triplet splitting of the C4 methylene (=CH–C$\underline{H}_2$) ^{13}C NMR signal (41.7 ppm, J 7.0 Hz). This phenomenon is characteristic for alkyl isonitriles. Similar spin ^{13}C–^{14}N coupling constants have been reported for analogous –C$\underline{H}_2$–N$\underline{C}$ systems.[7–10] Due to the electronic symmetry about the isonitrile nitrogen nucleus, coupling to the quadrupolar ^{14}N is observable. For this reason the ^{13}C NMR signal for a carbon next to an isonitrile appears as a triplet. As expected, a broad and partly split ^{13}C NMR signal was observed for the isonitrile carbon (–N$\underline{C}$ at 159.5 ppm) as well. In general, increasing temperature results in slower relaxation of the quadrupolar nucleus[11] and improves the coupling fine structure, observed as increased coupling constants. In contrast, reducing temperature would collapse the coupling. By increasing the temperature from 20 to 50 °C, we observed an increase of the ^{13}C–^{14}N NMR coupling constants for isonitrile **3**.

Table 1
J(C,H) and J(N,H) observed by HSQC and HMBC for compound **3**

	H_3	H_4	thi-H_2	thi-H_4	thi-H_5
C_1	^{3}J				
C_2	^{2}J	^{3}J	^{3}J	^{3}J	
C_3	^{1}J	^{2}J			
C_4	^{2}J	^{1}J			
C_5		^{3}J			
thi-C_2			^{1}J	^{3}J	^{3}J
thi-C_3	^{3}J		^{2}J	^{2}J	^{3}J
thi-C_4			^{3}J	^{1}J	^{2}J
thi-C_5			^{3}J	^{2}J	^{1}J
–CN					
–N$\underline{C}$	^{3}J	^{2}J			

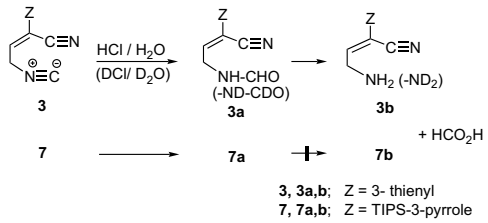
J_{C4-N} increased from 7.0 to 7.8 Hz and the broad singlet observed for –NC, turned into a triplet; J_{NC} 4.5 Hz, respectively.

(iv) HMBC $^{1}H-^{15}N$ NMR data confirmed the presence of an isonitrile function. Both H3 (CH=) and H4 (–CH_2) protons gave an ^{15}N correlation peak at 165 ppm (Table 1), characteristic for an isonitrile group (–NC, 150–200 ppm). As expected, H3 had no HMBC correlation with the nitrile (approx. 200–250 ppm), due to the longer distance between H3 and nitrile-CN.

(v) NOESY NMR spectroscopy of product **3** supported the 4-isocyano-2-thienylbut-2-enenitrile structure, since through-space proximity of the olefinic H3 and thienyl-H4 and -H2 was observed. In consequence, the data also indicate the less sterically hindered *Z*-configuration of the double bond in compound **3**.

(vi) Isonitriles undergo addition reactions by the addition of a nucleophile to the isonitrile carbon. Acid-catalysed hydrolysis of alkyl isonitriles has been examined and represents an addition reaction. Isonitriles are thus unstable in dilute aqueous acid. The initial hydrolysis product is the *N*-alkylformamide, which is further hydrolysed to the primary amine and formic acid at a slower rate.[12]

Compound **3** underwent such hydrolytic cleavage with treatment of isonitrile **3** with HCl/H_2O, monitored by ^{1}H NMR spectroscopy. The formamide intermediate **3a** was immediately formed and gradually, the amino degradation product **3b** was produced (Scheme 4). Depending on the amount of added HCl, quantitative conversion of **3** to amine **3b** was obtained in 2–30 h at room temperature. HRMS as well as ^{1}H and ^{13}C NMR data were in accordance with the amino structure **3b**. In particular, the increased shielding of H3 and H4 (=CH–CH_2, 0.3–0.4 ppm) and the disappearance of the isonitrile ^{13}C NMR signal (159.5 ppm) were typical for the reaction. When the reaction was carried out in DCl/D_2O, the amine ^{1}H NMR signals were not observed, due to deuteration (ND_2) in accordance with the mechanism. The hydrolytic degradation reactions were carried out in analytical scale. Product **3b** was unstable towards isomerisation by alkaline extraction and work-up.



Scheme 4.

2.3. Compound 4

HRMS data of the molecular ions of compound **3** and the other new product **4** confirmed their $C_9H_6N_2S$ composition. Strong nitrile IR absorption was observed for compound **4**. Product **4** was stable and isolated in 6% yield. ^{1}H NMR spectroscopy showed that the thien-3-yl group also was present in product **4**. However, the allylic methylene group from product **3** as well as typical pyridine protons from substrate **1** and product **2** was absent. The ^{1}H and ^{13}C NMR data fits entirely with the 2-(thien-3-yl)-pyrrole-3-carbonitrile structure **4** (Scheme 3). Assignments of all the NMR data were fully supported by 2D NMR experiments and confirmed that a ring contraction had taken place to give the stable aromatic 1*H*-pyrrole structure **4**. The pyrrole-NH of **4** is strongly hydrogen-bonded, as indicated by the high ^{1}H NMR N*H* frequency at 12.1 ppm. Due to the total aromaticity of the bis-aryl structure and the additional electron delocalisation, caused by the neighbouring conjugated cyano group, increased chemical shifts (approx. 0.3 ppm) of all thienyl protons of product **4** were observed relative to compound **3**.

NOESY experiments supported the structure of the 3-carbonitrile-3-thienylpyrrole **4**. The NOESY data left no doubt about the 2-thienyl-3-cyano-substitution pattern, since strong NOESY effects were observed between the pyrrole-NH and both thienyl-H2 and -H4.

2.4. Compound 7

Thermolysis of pyrrolopyridyl azide **5**[4] afforded the corresponding ring cleavage product as the former thienopyridyl azide **1**. 4-Isocyano-1-(2-TIPS-1*H*-pyrrol-3-yl)but-2-enenitrile (**7**, 20%) was isolated in addition to the main cyclisation product (**6**, 71%, Schemes 1 and 3). Triplet splitting was observed for both *C*H_2–N*C* ^{13}C NMR signals, due to the typical $^{13}C-^{14}N$ couplings of J_{CH2-N} 7.0 Hz and J_{NC} 4.5 Hz (20 °C). As seen for isonitrile **3**, the fine structure of these triplets was improved by increasing the temperature to 48 °C. Similar to product **3**, NOESY NMR data of product **7** supported the structure, showing the proximity of H3 and pyrrole-H4/-H2. Thus, compound **7** also seems to have *Z*-configuration.

Upon HCl treatment, isonitrile **7** did not undergo a complete degradation reaction to the amine **7b**, similar to the **3**–**3b** transformation. Instead, the formamide intermediate **7a** (Scheme 4) was isolated (95%). Due to the unpolar nature of the TIPS group, isonitrile **7** did not dissolve in HCl/H_2O and the reaction took place in a heterogeneous mixture. Thus, the effect of the acidic treatment was weaker than in the corresponding conversion of isonitrile **3**. Attempts to achieve full conversion of isonitrile **7** to the amine degradation product **7a** were made by carrying out the reaction in a homogeneous solution after addition of acetonitrile. However, all the pyrrole signals disappeared in the ^{1}H and ^{13}C NMR spectra, indicating decomposition of the pyrrole ring, due to the instability of pyrroles in acidic conditions.

NMR coupling patterns and shift values supported the formamide structure **7a**. The presence of the formamide CHO group was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The original ^{13}C NMR triplet observed for CH_2–NC of isonitrile **7**, as discussed above, was reduced to an ordinary singlet (CH_2–NH–CHO) in formamide **7a**. An HMBC ^{3}J-correlation between the indicated C–CH_2–NH–CH=O was observed.

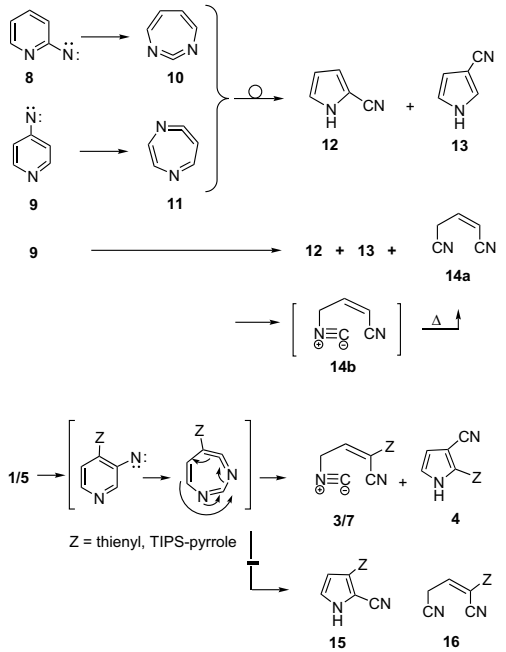
The IR spectra of **7** and **7a** were nearly identical, except for the lack of the strong isonitrile (2147 cm^{-1}) band and the respective appearance of a new amide-NH (3319 cm^{-1}) and a strong C=O (1668 cm^{-1}) stretch frequency in the **7a** spectrum. Both compounds **7** and **7a** showed the characteristic nitrile absorptions (2215 cm^{-1}).

When the reaction was carried out in DCl/D_2O, the aldehyde (CHO) and amide (NH–) ^{1}H NMR signals were not observed, due to deuteration (ND–CDO) in accordance with the mechanism. The CH–CH_2–ND signal appeared as a doublet, while the **7a** product formed by HCl hydrolysis showed a doublet of doublets for CH–CH_2–NH–.

2.5. Formation of products 3, 4 and 7

The chemistry of 2- and 4-pyridyl nitrenes (**8**, **9**) has previously been investigated. In particular, gas phase pyrolysis studies at above 450 °C were carried out..[13,14] The 2- and 4-pyridyl nitrenes both gave 2- and 3-cyanopyrroles (**12**, **13**), as shown in Scheme 5. The intermediate in the thermal interconversion was formulated as a seven-membered ring. The heteroarylnitrenes (**8**, **9**) underwent ring expansion and rearranged to diazacycloheptatetraenes; the carbodiimide **10** and the keteneimine **11**, in gas phase. Subsequent

ring contraction afforded the cyanopyrrole products **12** and **13**. By pyrolysis of **9** also minor amounts of the dicyano compound **14a** were formed.[13] In contrast, no studies were carried out on 3-pyridyl nitrenes.



Scheme 5.

If a corresponding mechanism takes place by the presently studied thermal decomposition of 3-pyridyl azides **1** and **5**, a diazaheptatetraene intermediate may be formed via the 3-pyridyl nitrene (Scheme 5). Subsequent ring contraction would explain the formation of minor amounts (6%) of the pyrrole product **4**, similar to **13**, from **1**. A ring opening mechanism, including a proton shift, would produce the nitrile isonitrile products **3** and **7**.

Neither tautomeric 2-cyano-3-thienylpyrrole **15** nor dicyano product **16**, similar to compounds **12** and **14a**, was observed. Isonitriles can however, rearrange thermally (>270 °C) into nitriles by pyrolysis.[19,20] Consequently, the previously reported dicyano product **14a** (Scheme 5)[13] may be formed by thermal rearrangement of an initially formed isonitrile–nitrile precursor **14b**, corresponding to the presently reported products **3** and **7**, due to the harsh pyrolysis conditions formerly used.

2.6. Isonitriles: occurrence, preparation and reactions

An increasing number of naturally occurring isonitrile compounds have been isolated. They have been reported to show a wide spectrum of biological, in particular antibiotic activity. Marine invertebrates and animals feeding on them contain isonitriles.[15–17]

Isonitriles are mostly prepared either by the reaction between alkyl halide and cyanide ion, by dehydration of *N*-alkylformamides or by reduction of isocyanides. The formation of cyclopentadienyl isonitriles by thermolysis of the appropriate azide precursors has once been reported. A nitrene mechanism including an intermediate aziridine ring opening is suggested.[18] However, no study of the ring cleavage of 3-pyridyl nitrenes for the formation of isonitriles has been carried out.

Isonitriles are used for synthetic transformations. In general, isonitriles readily undergo cyclisation reactions and these reactions provide useful methods for the preparation of five-membered heterocycles containing nitrogen, such as pyrroles, indoles, pyridazoles, oxazoles and thiazoles.[21] Isonitriles are simply oxidised to isocyanates with halogens and the polymers of isonitriles have a variety of applications. Isonitriles are used as ligands since they readily coordinate to metals. The organometallic syntheses of a series of metal isonitrile complexes and the reactions of these complexes have been studied.[22–25]

3. Conclusion

The present results demonstrate that 3-pyridyl azides may undergo thermal ring cleavage to form 4-isocyanobut-2-enenitrile products. Thermolysis of 4-(thien-3-yl)-3-pyridyl azide **1** and 3-azido-4-(1-TIPS-1*H*-pyrrol-3-yl)pyridine **5** afforded two new isonitrile–nitrile products by ring cleavage; 4-isocyano-2-(thiophen-3-yl)but-2-enenitrile (**3**, 27%) and 4-isocyano-2-(1-TIPS-1*H*-pyrrol-3-yl)but-2-enenitrile (**7**, 20%), in addition to our previously reported pyrido[3,4-*b*]thienopyrrole (**2**, 29%) and pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole (**6**, 71%) products. Minor amounts of 2-(thien-3-yl)-1*H*-pyrrole-3-carbonitrile (**4**, 6%), formed by ring contraction, were also isolated from thermolysis of azide **1**. Isonitriles **3** and **7** underwent degradation into, respectively, the amine **3b** and the formamide **7a** by acidic hydrolysis.

4. Experimental

4.1. General

Solvents: *pro analysi* quality. All reactions were performed under nitrogen atmosphere in pre-dried glassware. Flash column chromatography; SiO_2 (SDS, 60 Å, 40–63 μm). NMR: Bruker Avance DPX 300 and 400 MHz and Bruker DRX 600 MHz spectrometers. ^1H and ^{13}C chemical shifts are reported in parts per million downfield from TMS (or TSP-d_4 for compound **3b**). ^{15}N chemical shifts were referred indirectly to TMS, using absolute frequency ratios, and are reported in parts per million downfield from liquid ammonia.[26] *J* values are given in Hz. EIMS: Finnigan MAT 95 XL mass spectrometer (EI, 70 eV). ESI-MS accurate mass determination was performed on an Agilent 6520 QTOF MS instrument equipped with a dual electrospray ion source for continuous injection of mass axis calibrants through the second nebuliser needle. Samples were injected into the MS using an Agilent 1200 series HPLC and analysis was performed as a flow injection analysis without any chromatographic step. IR spectra were obtained with a Nicolet 20SXC FT-IR spectrophotometer. All melting points are uncorrected, measured on a Stuart apparatus. 3-Azido-4-(thien-3-yl)pyridine (**1**) and 3-azido-4-(1-TIPS-1*H*-pyrrol-3-yl)pyridine (**5**) were prepared according to literature.[1,4]

4.2. Preparation of 3 and 4

The title compounds were prepared from a solution of azide **1** (69 mg, 0.341 mmol) in *n*-decane (50 mL), by stirring at reflux (approx. 170 °C) for 30 min. The reaction mixture was allowed to cool to room temperature and decane was distilled off carefully. The crude product was purified by flash chromatography (CH_2Cl_2) to afford a mixture containing only **3** and **4** as an orange solid (21 mg, 35%). Use of internal standard (1,2,4,5-tetrachlorobenzene) confirmed the yield and gave the composition of **3** (17 mg, 29%) and **4** (4 mg, 6%). Increasing the polarity to 10% MeOH/CH_2Cl_2 afforded pyrido[3,4-*b*]thieno[2,3-*d*]pyrrole (**2a**).[1] Products **3** and **4** were individually isolated by flash chromatography (0.5% MeOH/CH_2Cl_2).

4.3. (*Z*)-4-Isocyano-2-(thiophen-3-yl)but-2-enenitrile (3)

The title compound was isolated as a yellow solid (16 mg, 27%), pure by NMR; R_f 0.37 (CH_2Cl_2); R_f 0.47 (0.5% MeOH/CH_2Cl_2); mp 61–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.60 (1H, dd, *J* 3.0, 1.2, thienyl-H2), 7.42 (1H, dd, *J* 5.1, 3.0, thienyl-H5), 7.26 (1H, dd, *J* 5.1, 1.2, thienyl-H4), 6.64 (1H, t, *J* 6.9, H3), 4.51 (2H, d, *J* 6.9, –CH_2, H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.5 (br s, CH_2–N<u>C</u>), 133.3 (thienyl-C3), 132.5 (C3), 128.2 (thienyl-C5), 125.8 (thienyl-C2), 123.8 (thienyl-C4), 114.9 (C2), 114.6 (CN, C1), 41.7 (t, *J* 7.0, <u>C</u>H_2–NC, C4); ^{1}H–^{15}N HMBC (600 MHz, $CDCl_3$) showed correlation between both H3/H4 and –*N*C (δ_N 165 ppm). NMR assignments are based on ATP, HSQC, NOESY and HMBC experiments; IR (KBr) ν_{max} 3080w, 2231w, 2154s, 1624w, 1437m, 1359w, 1276m, 1103w, 955m, 930m, 777s cm^{-1}; EIMS *m*/*z* (%) 174 (M^+, 100), 149 (38), 147 (48), 134 (12), 122 (52), 111 (29), 104 (14), 97 (21); ESI-HRMS calcd for $[M+Na]^+$ $C_9H_6N_2NaS$: 197.0143; obsd 197.0145; calcd for $[M+H]^+$ $C_9H_7N_2S$: 175.0324; obsd 175.0327.

4.4. (*Z*)-4-Amino-2-(thiophen-3-yl)but-2-enenitrile (3b)

Typical procedure for the formation of amine **3a**; isonitrile **3** (10 mg) was dissolved in 10% D_2O/H_2O (1 mL) in an NMR tube. HCl (concd, excess, approx. three drops) was added. Depending on the amount of added HCl, full conversion of **3** to amine **3a** was obtained in 2–30 h. The reaction was monitored by NMR; ^{1}H NMR (400 MHz, H_2O/D_2O/HCl) δ_H 8.31 (2H, br, NH_2), 7.75 (1H, dd, *J* 2.8, 1.2, thienyl-H2), 7.56 (1H, dd, *J* 5.2, 2.8, thienyl-H5), 7.42 (1H, dd, *J* 5.2, 1.2, thienyl-H4), 6.93 (1H, t, *J* 7.6, H3), 4.10 (2H, d, *J* 7.6, –CH_2; H4); ^{13}C NMR (100 MHz, H_2O/D_2O/HCl) δ_C 136.7 (C3), 136.3 (thienyl-C3), 131.3 (thienyl-C5), 128.8 (thienyl-C2), 127.3 (thienyl-C4), 118.4 (C2), 118.0 (-CN, C1), 42.7 (C4); NMR assignments are based on H,H-COSY, HSQC and HMBC experiments; ESI-HRMS calcd for $[M+H]^+$ $C_8H_9N_2S$: 165.0481; obsd 165.0480.

4.5. 2-(Thien-3-yl)-1*H*-pyrrole-3-carbonitrile (4)

The title compound was isolated as an orange oil (4 mg, 6%), pure by NMR; R_f 0.37 (CH_2Cl_2); R_f 0.40 (0.5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 12.1 (1H, br s, NH), 7.87 (1H, dd, *J* 2.8, 1.6, thienyl-H2), 7.72 (1H, dd, *J* 4.8, 2.8, thienyl-H5), 7.59 (1H, dd, *J* 4.8, 1.6, thienyl-H4), 6.97 (1H, dd, *J* 2.8, 2.8 pyrrole-H5), 6.53 (1H, dd, *J* 2.8, 2.4, pyrrole-H4); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 134.3 (pyrrole-C2), 131.0 (thienyl-C3), 127.7 (thienyl-C5), 125.0 (thienyl-C4), 121.5 (thienyl-C2), 119.9 (pyrrole-C5), 118.0 (CN), 112.1 (pyrrole-C4), 87.7 (pyrrole-C3); NMR assignments are based on H,H-COSY, HSQC, NOESY and HMBC experiments; IR (film) ν_{max} 3432br m, 2962w, 2215s, 1725s, 1653m, 1025s, 1006s, 790m cm^{-1}; ESI-HRMS calcd for $[M+H]^+$ $C_9H_7N_2S$: 175.0324; obsd 175.0324.

4.6. (*Z*)-4-Isocyano-2-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)but-2-enenitrile (7)

The title compound was prepared from **5** [4] as described for **3** above. Product **7** was separated from the main product **6** (71%) by flash chromatography (gradient: 0–10% MeOH/CH_2Cl_2) and obtained as a yellow solid (20%), pure by NMR; R_f 0.52 (CH_2Cl_2); mp 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.01 (1H, dd, *J* 2.0, 1.6, pyrrole-H2), 6.77 (1H, dd, *J* 2.8, 2.0, pyrrole-H5), 6.45 (1H, dd, *J* 2.8, 1.6, pyrrole-H4), 6.37 (1H, t, *J* 7.2, H3), 4.45 (2H, d, *J* 7.2, –CH_2, H4), 1.46 (3H, sept, *J* 7.6, C<u>H</u>(CH_3)$_2$), 1.10 (18H, d, *J* 7.6, CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 158.3 (t, $^1J_{CN}$ 4.5, CH_2–N<u>C</u>), 126.9 (C3), 126.8 (pyrrole-C5), 125.0 (pyrrole-C2), 119.6 (pyrrole-C3), 115.3 (C1, CN), 114.4 (C2), 107.2 (pyrrole-C4), 41.7 (t, *J* 7.0, CH_2–NC), 17.7 (TIPS-*C*H_3). 11.5 (TIPS–*C*H); NMR assignments are based on HSQC, HMBC and NOESY experiments; IR (film) ν_{max} 2948s, 2869s, 2215w, 2147s, 1624m, 1491m, 1463m, 1264m, 1227m, 1130s, 1097s, 884s, 795s cm^{-1}; ESI-HRMS calcd for $[M+Na]^+$ $C_{18}H_{27}N_3NaSi$: 336.1867; obsd 336.1882.

4.7. (*Z*)-*N*-(3-Cyano-3-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)allyl)-formamide (7a)

HCl (1.0 mL, concd) and H_2O (1.0 mL) were added to compound **7** (10.0 mg, 31.9 μmol) to form a heterogeneous mixture. The original solid turned into a brown oil after 1 h. Water (10.0 mL) was added and the oil was dissolved in CH_2Cl_2 (20 mL). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The product was obtained as a brown oil (10 mg, 95%). Full conversion of **7** into compound **7a** was obtained as shown by NMR; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.24 (1H, s, *C*H=O), 6.97 (1H, dd, *J* 2.8, 1.2, pyrrole-H2), 6.74 (1H, dd, *J* 2.8, 2.0, pyrrole-H5), 6.46 (1H, t, *J* 7.2, =*CH*–), 6.42 (1H, dd, *J* 2.8, 1.6, pyrrole-H4), 5.85 (1H, s, br, NH), 4.31 (2H, dd, *J* 7.2, 6.4, C<u>H</u>$_2$–NH), 1.45 (3H, sept, *J* 7.6, *CH*(CH_3)$_2$), 1.10 (18H, d, *J* 7.6, CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.0 (*C*H=O), 132.8 (=*C*H–), 126.4 (pyrrole-C5), 124.0 (pyrrole-C2), 120.3 (pyrrole-C3), 116.4 (CN), 112.8 (CH=<u>C</u>–CN), 107.2 (pyrrole-C4), 38.2 (CH_2–NH), 17.7 (TIPS-*C*H_3), 11.5 (TIPS-*C*H); NMR assignments are based on HSQC and HMBC experiments; IR (film) ν_{max} 3319br, 2947s, 2868s, 2219w, 1668s, 1464m, 1385m, 1227m, 1132s, 1098s, 1017m, 884s cm^{-1}; ESI-HRMS calcd for $[M+H]^+$ $C_{18}H_{30}N_3OSi$: 332.2152; obsd 332.2161; calcd for $[M+Na]^+$ $C_{18}H_{29}N_3ONaSi$: 354.1972; obsd 354.1978.

Acknowledgements

Trygve Andreassen (Ph.D.), NMR-centre, NT-faculty, NTNU, is acknowledged for his NMR technical assistance.

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Paper IV

Lars Kr. Hansen, Vegar Stockmann and Anne Fiksdahl

8*H*-6-Azathieno[2,3-*b*]indole

Cambridge Crystallographic Data Center. http://www.ccdc.cam.ac.uk (accessed Oct 2010), deposition number: CCDC 778181. To be published in *Acta Crystallogr.,Sect. E: Struct. Rep. Online*.

8*H*-6-Azathieno[2,3-*b*]indole

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The title compound, 8*H*-6-aza-thieno[2,3-*b*]indole (I), $C_9H_6N_2S$, consists of three fused heterocyclic rings. The N—H group is involved in an N—H···N intermolecular hydrogen bond.

Experimental

Crystal data

$C_9H_6N_2S$
$M_r = 174.22$
Orthorhombic, *Fdd*2
$a = 15.191$ (4) Å
$b = 41.704$ (11) Å
$c = 4.9942$ (12) Å
$V = 3164.0$ (14) Å^3
$Z = 16$
Mo $K\alpha$ radiation, $\lambda = 0.71070$ Å
$\mu = 0.34$ mm^{-1}
$T = 293$ K
0.60 × 0.15 × 0.10 mm

Data collection

Rigaku Saturn diffractometer
Absorption correction: Multi-scan Jacobson, R. (1998) Private communication
$T_{min} = 0.929$, $T_{max} = 0.973$
2328 measured reflections
1446 independent reflections
1244 reflections with $F^2 > 2.0\sigma(F^2)$
$R_{int} = 0.016$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$
$wR(F^2) = 0.041$
$S = 1.04$
1251 reflections
133 parameters
All H-atom parameters refined
$\Delta\rho_{max} = 0.23$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H3···N3^{i}	0.89 (3)	1.92 (3)	2.796 (3)	168 (3)
C1—H1···S1^{ii}	0.96 (3)	3.40 (3)	3.558 (3)	90 (2)
C2—H2···S1^{ii}	1.00 (2)	3.53 (3)	3.590 (3)	85.1 (15)

Data collection: *CrystalClear*; cell refinement: *CrystalClear*; data reduction: *CrystalStructure*; program(s) used to solve structure: *SHELXS97*; program(s) used to refine structure: *CRYSTALS*; software used to prepare material for publication: *CrystalStructure* 3.7.0.

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supplementary materials

8*H*-6-Azathieno[2,3-*b*]indole

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Comment

The β-carboline ring structure (II) is incorporated into many natural products and pharmaceuticals, and a series of pharmacological effects of β-carboline alkaloids have lately been studied by Bartel (2006), Bi *et al.* (2006), Garcia *et al.* (2006), Guan *et al.* (2006), Ichikawa *et al.* (2006), Winkler *et al.* (2006) and Zhao *et al.* (2006).

We have prepared and studied the new β-carboline thiophene analogue, the title compound (I), due to its potential biological activity (Stockmann & Fiksdahl, 2008). For X-ray studies of β-carboline (II, 9H-pyrido[3,4-b]indole) and derivatives, see Arbain (1990), Dodd (1987), Feretti (2004), Holt (1990), Muir (1985), Nakamura (1987), Pal *et al.* (2004) and Ray (1957). For related literature on thienoindole derivatives, see Bocellini *et al.* (1990), Janosik *et al.* (2002), Kanbe *et al.* (1993), Levy *et al.* (1987).

The crystal structure of I was solved as part of this study. A view of the title molecule with the atomic numbering scheme is presented in Fig 1. The bond lengths are within the normal range of such bonds (Allen *et al.*, 1987) and also in accordance with the regio-isomer 7-azathieno[3,2-c]cinnoline (Hansen *et al.*, 2007) and other benzo[c]cinnoline derivatives (Hökelek *et al.*, 1990, 1991a,1991b). The C6—C7 bonds are always significantly shorter than the C7—C8 bonds. Mean C6—C7 bond is 1.370 (4)Å while the mean C7—C8 bond is 1.402 (4) Å. (see Van der Meer,1972 and references cited therein).

Experimental

The new pyrido[3,4-*b*]thieno[3,2-*d*]pyrrole (I) was prepared from 3-aminopyridine in six steps by the Suzuki - nitrene approach. The β-carboline thiophene analogue (I) was obtained by thermal decomposition of the 3-azido-4-(thiophene-3-yl)pyridine precursor and subsequent cyclisation via the nitrene intermediate. Compound I was dissolved in methanol. Single crystals suitable for x-ray analysis were grown by mixed-solvent crystallisation (methanol light petroleum/40-60 C) by slow diffusion between the two layers at -18 C (Stockmann & Fiksdahl, 2008).

Refinement

All H atoms were found from a difference map and were refined isotropically.

Crystal data

$C_9H_6N_2S$	$F(000)$ = 1440.00
M_r = 174.22	D_x = 1.463 Mg m^{-3}
Orthorhombic, *Fdd*2	Mo *K*α radiation, λ = 0.71070 Å
Hall symbol: F 2 -2d	Cell parameters from 1835 reflections

a = 15.191 (4) Å	θ = 2.9–30.4°
b = 41.704 (11) Å	μ = 0.34 mm^{-1}
c = 4.9942 (12) Å	T = 293 K
V = 3164.0 (14) Å^3	Needle, Colourless
Z = 16	0.60 × 0.15 × 0.10 mm

Data collection

Rigaku Saturn diffractometer	1244 reflections with $F^2 > 2.0\sigma(F^2)$
Detector resolution: 7.31 pixels mm^{-1}	R_{int} = 0.016
ω scans	θ_{max} = 30.4°
Absorption correction: Multi-scan Jacobson, R. (1998) Private communication	h = −21→21
T_{min} = 0.929, T_{max} = 0.973	k = −55→55
2328 measured reflections	l = −6→6
1446 independent reflections	

Refinement

Refinement on F	All H-atom parameters refined
$R[F^2 > 2\sigma(F^2)]$ = 0.035	Chebychev polynomial *w*ith 3 parameters (Carruthers & Watkin, 1979) 107.7680 128.7040 42.8525
$wR(F^2)$ = 0.041	$(\Delta/\sigma)_{max}$ = 0.001
S = 1.04	$\Delta\rho_{max}$ = 0.23 e Å^{-3}
1251 reflections	$\Delta\rho_{min}$ = −0.23 e Å^{-3}
133 parameters	

Special details

Geometry. ENTER SPECIAL DETAILS OF THE MOLECULAR GEOMETRY

Refinement. Refinement using reflections with $F^2 > 2.0$ sigma(F^2). The weighted R-factor(wR), goodness of fit (S) and R-factor (gt) are based on F, with F set to zero for negative F. The threshold expression of $F^2 > 2.0$ sigma(F^2) is used only for calculating R-factor (gt).

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}
S1	0.47768 (5)	0.70399 (2)	0.2023 (2)	0.04314 (17)
N1	0.40225 (17)	0.65868 (6)	0.5599 (6)	0.0451 (6)
N3	0.23285 (19)	0.64464 (6)	1.0751 (6)	0.0518 (7)
C1	0.42635 (18)	0.74100 (6)	0.2425 (6)	0.0416 (7)
C2	0.36323 (16)	0.74113 (6)	0.4330 (6)	0.0369 (6)
C3	0.41117 (16)	0.68834 (6)	0.4471 (6)	0.0368 (6)
C4	0.33463 (18)	0.66101 (6)	0.7426 (6)	0.0399 (7)
C5	0.2985 (2)	0.63790 (6)	0.9069 (7)	0.0498 (9)
C6	0.2022 (2)	0.67482 (6)	1.0818 (7)	0.0479 (8)
C7	0.23377 (18)	0.69954 (6)	0.9286 (7)	0.0407 (7)
C8	0.30219 (17)	0.69296 (6)	0.7484 (5)	0.0353 (6)
C9	0.35316 (17)	0.71038 (6)	0.5549 (6)	0.0340 (6)
H1	0.447 (2)	0.7587 (7)	0.136 (8)	0.062 (10)*
H2	0.3248 (17)	0.7596 (6)	0.485 (6)	0.040 (7)*
H3	0.430 (2)	0.6409 (9)	0.508 (8)	0.078 (12)*

H5	0.318 (2)	0.6167 (7)	0.899 (7)	0.047 (8)*
H6	0.157 (2)	0.6793 (7)	1.199 (7)	0.050 (8)*
H7	0.2075 (19)	0.7208 (7)	0.940 (7)	0.048 (8)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0414 (3)	0.0473 (3)	0.0407 (3)	0.0001 (2)	0.0068 (3)	−0.0010 (3)
N1	0.0521 (13)	0.0328 (11)	0.0503 (15)	0.0062 (9)	0.0138 (12)	−0.0018 (11)
N3	0.0571 (15)	0.0444 (12)	0.0540 (16)	−0.0090 (11)	0.0085 (13)	0.0089 (13)
C1	0.0393 (13)	0.0437 (14)	0.0419 (17)	−0.0037 (10)	−0.0009 (14)	0.0055 (13)
C2	0.0340 (11)	0.0361 (12)	0.0406 (15)	0.0012 (9)	−0.0016 (13)	0.0034 (12)
C3	0.0382 (12)	0.0347 (11)	0.0375 (14)	−0.0001 (9)	0.0001 (13)	−0.0033 (12)
C4	0.0435 (13)	0.0337 (12)	0.0424 (17)	−0.0025 (9)	0.0036 (13)	−0.0018 (12)
C5	0.0607 (18)	0.0327 (12)	0.056 (2)	−0.0041 (11)	0.0036 (17)	0.0058 (14)
C6	0.0498 (16)	0.0482 (16)	0.0456 (17)	−0.0045 (12)	0.0109 (15)	−0.0004 (15)
C7	0.0392 (13)	0.0405 (13)	0.0425 (15)	0.0009 (10)	0.0045 (13)	0.0001 (14)
C8	0.0370 (11)	0.0335 (11)	0.0352 (16)	−0.0024 (9)	−0.0003 (11)	−0.0036 (11)
C9	0.0331 (11)	0.0363 (12)	0.0325 (13)	0.0013 (9)	−0.0003 (10)	0.0007 (11)

Geometric parameters (Å, º)

S1—C1	1.741 (3)	C4—C8	1.421 (3)
S1—C3	1.715 (3)	C6—C7	1.370 (4)
N1—C3	1.366 (3)	C7—C8	1.402 (4)
N1—C4	1.378 (4)	C8—C9	1.436 (3)
N3—C5	1.334 (4)	N1—H3	0.89 (3)
N3—C6	1.342 (3)	C1—H1	0.96 (3)
C1—C2	1.351 (4)	C2—H2	1.00 (2)
C2—C9	1.428 (3)	C5—H5	0.94 (3)
C3—C9	1.382 (3)	C6—H6	0.93 (3)
C4—C5	1.380 (4)	C7—H7	0.97 (3)
C1—S1—C3	89.51 (13)	C7—C8—C9	137.1 (2)
C3—N1—C4	106.5 (2)	C2—C9—C3	111.3 (2)
C5—N3—C6	118.2 (2)	C2—C9—C8	143.1 (2)
S1—C1—C2	113.7 (2)	C3—C9—C8	105.6 (2)
C1—C2—C9	111.9 (2)	C3—N1—H3	126 (2)
S1—C3—N1	134.2 (2)	C4—N1—H3	127 (2)
S1—C3—C9	113.6 (2)	S1—C1—H1	118 (2)
N1—C3—C9	112.2 (2)	C2—C1—H1	128 (2)
N1—C4—C5	129.9 (2)	C1—C2—H2	126.9 (17)
N1—C4—C8	109.8 (2)	C9—C2—H2	121.2 (17)
C5—C4—C8	120.3 (2)	N3—C5—H5	118 (2)
N3—C5—C4	121.6 (2)	C4—C5—H5	121 (2)
N3—C6—C7	124.8 (3)	N3—C6—H6	117.7 (19)
C6—C7—C8	118.1 (2)	C7—C6—H6	117.5 (19)
C4—C8—C7	117.0 (2)	C6—C7—H7	120.5 (19)
C4—C8—C9	105.9 (2)	C8—C7—H7	121 (2)
C1—S1—C3—N1	179.3 (3)	N1—C3—C9—C8	−1.2 (3)

C1—S1—C3—C9	−0.4 (2)	N1—C4—C5—N3	179.5 (3)
C3—S1—C1—C2	0.6 (2)	N1—C4—C8—C7	−178.9 (2)
C3—N1—C4—C5	178.9 (3)	N1—C4—C8—C9	0.7 (3)
C3—N1—C4—C8	−1.4 (3)	C5—C4—C8—C7	0.7 (4)
C4—N1—C3—S1	−178.0 (2)	C5—C4—C8—C9	−179.6 (2)
C4—N1—C3—C9	1.6 (3)	C8—C4—C5—N3	−0.1 (3)
C5—N3—C6—C7	−0.3 (5)	N3—C6—C7—C8	0.9 (5)
C6—N3—C5—C4	−0.1 (4)	C6—C7—C8—C4	−1.1 (4)
S1—C1—C2—C9	−0.6 (3)	C6—C7—C8—C9	179.4 (3)
C1—C2—C9—C3	0.3 (3)	C4—C8—C9—C2	177.9 (3)
C1—C2—C9—C8	−177.2 (3)	C4—C8—C9—C3	0.3 (3)
S1—C3—C9—C2	0.1 (2)	C7—C8—C9—C2	−2.6 (6)
S1—C3—C9—C8	178.6 (2)	C7—C8—C9—C3	179.8 (3)
N1—C3—C9—C2	−179.6 (2)		

Hydrogen-bond geometry (Å, º)

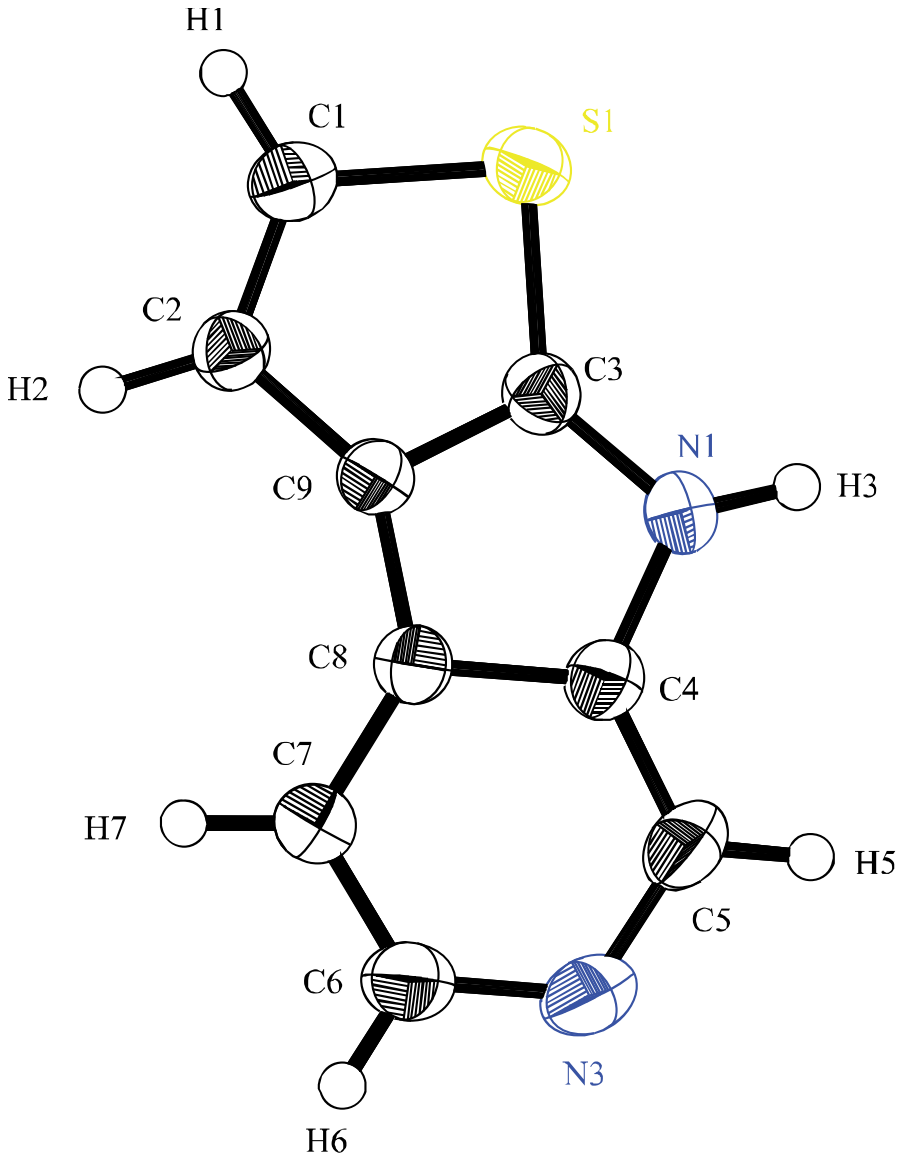
D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H3···N3^{i}	0.89 (3)	1.92 (3)	2.796 (3)	168 (3)
C1—H1···S1^{ii}	0.96 (3)	3.40 (3)	3.558 (3)	90 (2)
C2—H2···S1^{ii}	1.00 (2)	3.53 (3)	3.590 (3)	85.1 (15)

Symmetry codes: (i) *x*+1/4, −*y*+5/4, *z*−3/4; (ii) −*x*+1, −*y*+3/2, *z*+1/2.

Figure 1

Fig. 1. A view of the title compound with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

Fig. 1



Paper V

Lars Kr. Hansen, Vegar Stockmann and Anne Fiksdahl

7-Azathieno[3,2-*c*]cinnoline

Acta Crystallogr., Sect. E: Struct. Rep. Online **2007**, *E63*, o3290.

Is not included due to copyright

Paper VI

Lars Kr. Hansen, Vegar Stockmann and Anne Fiksdahl

7-Azathieno[2,3-*c*]cinnoline

Acta Crystallogr., Sect. E: Struct. Rep. Online **2007**, *E63*, o3896.

Is not included due to copyright

Paper VII

7-Azacinnolin-4(1*H*)-one; preparation and NMR-studies of tautomery

Vegar Stockmann, Sebastian Primpke and Anne Fiksdahl

J. Heterocyclic Chem. **2010**, accepted.

Month 2010

7-Azacinnolin-4(1*H*)-One Preparation and NMR Studies of Tautomery

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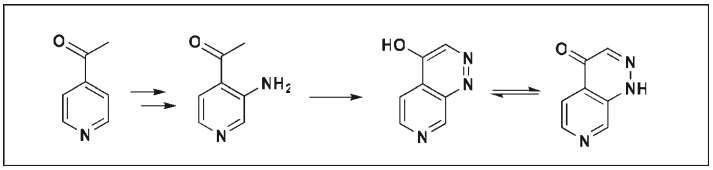
Received April 13, 2010
DOI 10.1002/jhet.580
Published online 00 Month 2010 in Wiley Online Library (wileyonlinelibrary.com).



As part of our current investigations of nitropyridines, we hereby report the preparation of a new annulated heterocycle by C-azo coupling. Thus, the azacinnoline, pyrido[3,4-c]pyridazin-4(1*H*)-one (38%), was prepared from 4-acetyl-3-aminopyridine via diazotization. ^{1}H, ^{13}C, and ^{15}N NMR spectroscopic investigations revealed that the azacinnoline exclusively exists in the NH-keto tautomeric form in DMSO-d_6, CD_3OD, and D_2O.

J. Heterocyclic Chem., **00**, 00 (2010).

INTRODUCTION

Investigations on the chemistry of nitropyridines are currently in progress in our laboratories, based on the fact that a number of substituted 3-nitropyridines have become readily available through an improved nitration method [1,2]. We have previously reported the preparation of the new pyrido[3,4-c]thieno[3,2-e]pyridazine (**I**, X = S, Scheme 1) by diazo-coupling [3]. The furan and pyrrole products (**I**, X = O, NH) were also prepared in a similar manner [4]. The results demonstrated that the diazonium intermediate pathway readily allows the synthesis of pyridine-fused azo-coupling compounds from nitropyridines.

Pyridopyridazines (**II**) have been studied for preventing and treating atherosclerosis [5] and such heterocycles are also used as substrates for the preparation of antiviral agents [6]. Furthermore, other pyridazine compounds are biologically active, and the pyridazine moiety is incorporated in a series of pharmaceuticals. Cinnolines (**III**, Scheme 1) [7] are important intermediates in the preparation of the antidepressant binodaline [8] and the antibiotic cinoxacin [9]. A series of substituted benzo[c]cinnolines (**IIIa**) show herbicidal activity [10], whereas others are mutagenic substances [11], being identified as organic aza-heterocyclic pollutants [12]. The corresponding *N*-analogous pyrido[3,4-*c*]cinnoline (**IIIb**) ring structure has also been reported [13]. Cinnolin-4-ol (**IVa**) is used as a drug intermediate [14] and is a precursor for the preparation of potential antimalarial drugs and herbicides [15]. Recently, a detailed NMR study on the tautomerism of the benzo-fused heterocycle **IVa** has been reported [16]. It was concluded that this compound exists as the NH-keto isomer **IVb** in DMSO-d_6.

In contrast to the well-studied cyclization reaction to afford the cinnoline IVb (Scheme 1) by diazotization and C-azo-coupling, the corresponding preparation of the novel pyridine-analogue 2 (Scheme 2) has received hardly any attention. An early investigation reported an unsuccessful ring-closure of 4-acetyl-3-aminopyridine (5) after diazotization [17]. Applying either acidic or basic conditions, no products, arising from cyclization, could be observed or isolated.

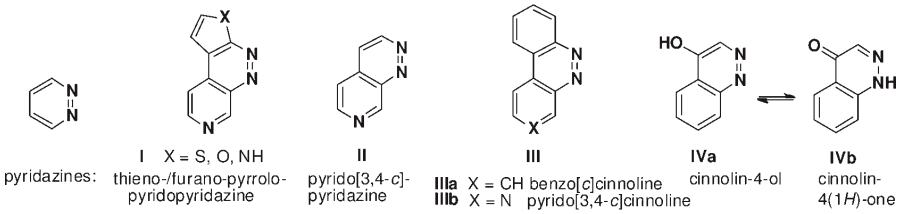
Because of the potential biological activity, the therapeutic use and the generally interesting properties of cinnolines, we wanted to prepare the new and previously unknown 7-azacinnolin-4-(1*H*)-one (2) (Scheme 2), being a pyridine-analogue of the benzo-fused cinnoline IVb (Scheme 1). The 4-substituted pyridyl diazonium salt 1 is readily prepared from the appropriate nitropyridine 4 via pyridylamine 5. The following cyclization of diazonium intermediate 1 by intramolecular C-azo-coupling has been investigated, and the successful preparation of aza-cinnoline derivative 2 is hereby reported. The tautomerism of azacinnoline (2/2′) has been studied by ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy.

RESULTS AND DISCUSSION

The three-step synthesis for the preparation of azacinnoline **2** is shown in Scheme 2.

The nitropyridine derivative **4** is reported to be available in 75% yield by nitration of 4-acetylpyridine (**3**),

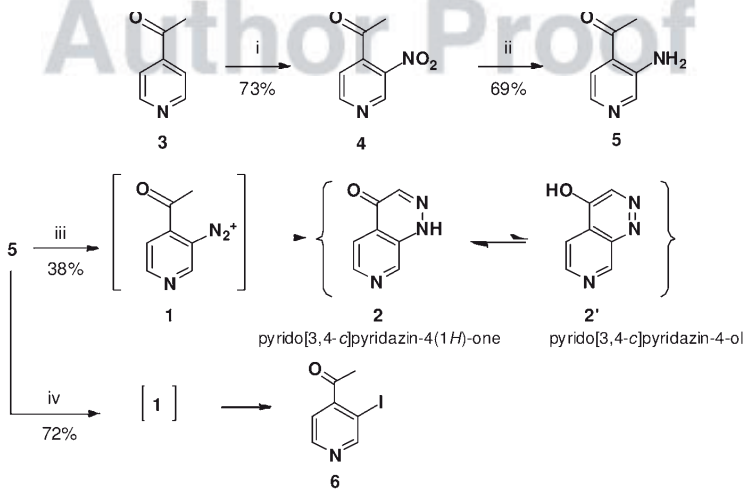
Scheme 1



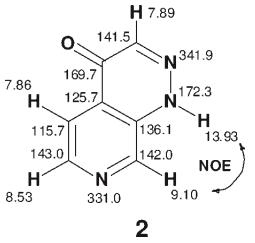
using dinitrogen pentoxide (N_2O_5, DNP) as the nitrating agent in liquid SO_2. The reaction mixture is poured into water before work-up [18]. By a considerably simpler procedure, yielding 58% of nitro-compound **4**, the pyridine is reacted with DNP in $MeNO_2$. The reaction mixture is poured into a solution of $NaHSO_3$ in MeOH-H_2O (3:1) before product isolation [18]. By minor adjustments of the latter procedure, mainly by increasing the reaction time and by precooling the $NaHSO_3$-MeOH/H_2O solution, we were able to increase the yield of 4-acetyl-3-nitropyridine (**4**) from 58 to 73%, comparable to the former SO_2-H_2O procedure. The nitropyridine **4** was reduced with sodium hyposulfite [19] to prevent reduction of the ketone. Amine **5** was obtained in 69% yield, as reported in the literature [20]. Reduction with H_2/Pd or $Pd(OAc)_2$/Et_3SiH gave considerably lower yields (32–39%).

The preparation of azacinnoline **2** was based on the Borsche approach [21] for the synthesis of cinnolin-4(1*H*)-one (**IVb**) from 2-aminoacetophenone. Diazotization of amine **5** with HCl/$NaNO_2$ in EtOH and subsequent cyclization in alkalic medium by addition of NaOH in EtOH/H_2O afforded the azo-coupling product **2** (38%). Several attempts to optimize the reaction conditions by applying different alkalic systems for the cyclization, such as NaOH (aq), $NaHCO_3$ (aq, sat), phosphate buffer (pH 7.5), and Et_3N, afforded lower yield of product **2**. The following conditions were critical to obtain successful cyclisation. Initially, when applying standard diazotization conditions ($NaNO_2$/HCl/H_2O), we were only able to isolate low yields (<10%) of product **2**. The yield increased significantly by using EtOH as a solvent for the diazotization. Cyclization was favored at pH 7–10. The temperature should strictly be kept below 0°C while adding the basic solution to avoid formation of the 4-acetylpyridine reduction product **3**. It was essential to treat the solution of diazonium salt **1** with the basic solution for successful cyclization, as the opposite treatment only afforded traces amounts of product **2**. Ether extraction at pH 12 removed traces of amine **5**

Scheme 2



Reagents and conditions: (i) 1. N_2O_5 in $MeNO_2$, 0 °C, 2. $NaHSO_3$ in MeOH/H_2O; (ii) $Na_2S_2O_4$ in EtOH, reflux, 6 h; (iii) 1. $NaNO_2$ in HCl/H_2O/EtOH, 0 °C, 2. NaOH in H_2O/EtOH, -10 °C; (iv) 1. $NaNO_2$ in p-TsOH/H_2O, 2. KI



2

Figure 1. ^{1}H, ^{13}C, and ^{15}N NMR spectroscopic data of pyridopyridazin-4-one **2** (DMSO-d_6).

and by-product **3**, leaving product **2** in the aqueous phase. The product was afforded by repeated extraction with EtOAc at pH 4–8. Complete product extraction was controlled by TLC monitoring.

A recent report on the iodination of aryl amines in a water-paste form via stable aryl diazonium tosylates [22] demonstrates a simple and effective procedure for the preparation of various aryl iodides. This diazotization method was successfully tested for preparing diazonium ion intermediate **1** to produce 4-acetyl-3-iodopyridine (**6**) from amino-pyridine **5** in high yield (72%). Unfortunately, this method was less successful when applied for the presently studied intramolecular C-azo-coupling of diazonium ion **1**. Only 20% yield of cyclization product **2** was obtained, using a phosphate buffer (pH 7.5) at 0°C for the cyclisation of aryl diazonium tosylate (**1**).

Prototropic tautomerism of heteroaromatic compounds has been studied for decades and is of great biological interest, due to the importance of hydrogen bondings in biological systems [23]. A mixture of compounds **2** and **2′** (Scheme 2) would represent a ketone–phenol tautomeric equilibrium. In general, for simple phenols, the equilibrium lies to the side of phenol to retain the aromatic system. It is, however, well known that the keto form predominates and may be the only detectable form in heterocyclic systems in solution.

NMR spectroscopic investigations revealed that the aza-cinnoline product exists as the keto tautomeric form **2** in DMSO-d_6, in accordance with similar results reported for the benzo-fused cinnoline **IVb** [16]. In general, all NMR data, including results obtained by detailed 2D NMR correlation experiments, ATP, NOESY, HSQC, and HMBC, were in agreement with the NH-keto structure **2**. The NMR signals (δ_H, δ_C, and
F1 δ_N) were assigned based on the 2D experiments (Fig. 1). δ_N-Values, reported downfield from liquid ammonia, were obtained from ^{1}H-^{15}N HMBC experiments.

The ^{13}C NMR spectrum of compound **2** showed a characteristic carbonyl signal at 169.7 ppm, in accordance with C4 in the keto-structure **2**. A potential =C—OH signal from the phenolic tautomer **2′** would be expected to appear at higher field. NOESY experiments demonstrated that the acidic proton at 13.93 ppm, represented the =N—NH moiety in compound **2** and not a potential phenolic OH from **2′**, since a through-space proximity between the acidic H1 (13.93 ppm) and H8 (9.10 ppm) was observed. The structure was unambiguously confirmed by heteronuclear multiple bond correlation (HMBC) experiments. The δ_N-values were assigned by heteronuclear long-range correlation ($^{2}J_{N\text{-}H}$ and $^{3}J_{N\text{-}H}$) both between N1 (172.3 ppm) and protons H3, H8; between N2 (341.9 ppm) and proton H3; and between N7 (331.0 ppm) and protons H5, H6, H8. These results left no doubt concerning the keto tautomeric form **2** of the aza-cinnoline product. In particular, the presence of the =N—NH— structure moiety of **2** was confirmed by the essentially different shift values of N1 and N2. The phenol tautomeric form **2′** would have more similar chemical shifts for N1 and N2, due to the presence of a N=N double bond. The chemical shift values for N1 and N2 are in accordance with the reported ^{15}N chemical shifts for cinnolin-4(1*H*)-one (**IVb**) [16]. $CDCl_3$ was not suitable as solvent, as 7-azacinnoline **2** was nearly insoluble in nonpolar solvents. Similar ^{1}H and ^{13}C NMR chemical shift values were observed for azacinnoline **2** in polar protic solvents, such as D_2O and CD_3OD, as in DMSO-d_6. The presence of the carbonyl signal for C4 in CD_3OD (174.0 ppm) and in D_2O (174.6 ppm), confirmed that the keto tautomeric form **2** exclusively dominates in these solvents as well.

In conclusion, pyrido[3,4-c]pyridazin-4(1*H*)-one (**2**) has successfully been prepared by an intramolecular C-azo-coupling, to the best of our knowledge, for the first time. Nitration of 4-acetylpyridine (**3**), reduction, and subsequent diazotization afforded the cyclic azacinnoline product **2**. Based on detailed 2D NMR studies, it was concluded that compound **2** exclusively exists in the NH-keto tautomeric form in DMSO-d_6, CD_3OD, and D_2O.

EXPERIMENTAL

General. Solvents: *pro analysi* quality. NMR: Bruker Avance DPX 400 MHz and Bruker DRX 600 MHz spectrometers. ^{1}H and ^{13}C NMR chemical shift values are reported in ppm downfield from TMS for samples in DMSO-d_6 or $CDCl_3$ and downfield from 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS) for samples in CD_3OD or D_2O. *J* values are given in Hz. ^{15}N chemical shifts were referenced indirectly to TMS, using absolute frequency ratio, and are reported in ppm downfield from liquid ammonia [24]. ESI-HRMS accurate mass determination was performed on a Waters QTOF II instrument. IR: Nicolet 20SXC FT-IR spectrophotometer equipped with a Smart Endurance reflexion cell. All melting points are uncorrected and were recorded on a Stuart

apparatus. Flash column chromatography; SiO_2 SDS, 60 Å, 40–63 μm.

Pyrido[3,4-c]pyridazin-4(1*H*)-one (2). To a solution of **5** (106 mg, 0.779 mmol) in ethanol (4 mL) and HCl (conc, 2 mL) at 0°C, an ice-cold solution of $NaNO_2$ (70 mg, 1.01 mmol) in water (1 mL) was added dropwise within 20 min. The reaction mixture was stirred for 1 h and cooled to −10°C. From an ice-cold solution of NaOH (1.08 g, 27 mmol) in H_2O (5 mL)/EtOH (10 mL), the required amount (~24 mmol NaOH) was added drop-wise over 1 h to give pH 8. The reaction was kept stirring for 2 h at −10°C, keeping pH 8–10 by adding additional NaOH/H_2O/EtOH solution. The remaining NaOH/EtOH/H_2O solution was added to give pH 14, and the reaction was allowed to heat to room temperature before water (15 mL) was added. The aqueous solution was washed with ether (10 mL) and acidified with HCl (1*M*) to give pH 4–6. Extraction with EtOAc (6 × 20 mL), drying over Na_2SO_4, evaporation of solvent and flash chromatography (gradient: 5–10% MeOH/CH_2Cl_2) afforded 43 mg (38%) of the title compound **2** as a light orange solid, mp 263–264°C, pure by NMR: R_f 0.37 (10% MeOH/CH_2Cl_2); IR: 2827, 1601, 1561, 1445, 1314, 1081, 881, 853 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6): δ_H 13.93 (br s, 1H, NH), 9.10 (d, J = 0.8 Hz, 1H, H8), 8.53 (d, J = 5.6 Hz, 1H, H6), 7.89 (s, 1H, H3), 7.86 (dd, J = 5.6, 0.8 Hz, 1H, H5); ^1H NMR (400MHz, CD_3OD): δ_H 9.08 (s, 1H, H8), 8.52 (d, J = 5.2 Hz, 1H, H6), 7.97 (dd, J = 5.2, 1.2 Hz, 1H, H5), 7.92 (s, 1H, H3); ^1H NMR (400 MHz, D_2O): δ_H 9.16 (s, 1H, H8), 8.53 (d, J = 6.0 Hz, 1H, H6), 8.05 (s, 1H, H3), 7.95 (dd, J = 6.0, 0.8 Hz, 1H, H5); ^{13}C NMR (100MHz, DMSO-d_6): δ_C 169.7 (C=O), 143.0 (py-C6), 142.0 (py-C2), 141.5 (CH=N), 136.1 (py-C3), 125.7 (py-C4), 115.7 (py-C5); ^{13}C NMR (100MHz, CD_3OD): δ_C 174.0, 145.8, 144.8, 144.6, 139.8, 129.2, 119.2; ^{13}C NMR (100MHz, D_2O): δ_C 174.6, 145.4, 145.2, 143.9, 139.2, 128.8, 118.9; ^{15}N chemical shifts were obtained from ^1H-^{15}N HMBC experiments (600 MHz, DMSO-d_6): δ_N 341.9 (N2), 331.0 (N7), 172.3 (N1); NMR assignments are based on HMBC, HSQC, and NOESY experiments; ESI-HRMS: calcd for $[M+H]^+$ $C_7H_6N_3O$: 148.0505; obsd 148.0505; calcd for $[M+Na]^+$ $C_7H_5N_3NaO$: 170.0325; obsd 170.0321.

4-Acetyl-3-nitropyridine (4). Nitropyridine **4** was prepared from 4-acetylpyridine (**3**) as described elsewhere [18], except for minor modifications. Dinitrogen pentoxide (DNP) was prepared from dinitrogen tetroxide and ozone [25]. DNP (10.0 g, 92.6 mmol) was kept at −78°C and $MeNO_2$ (100 mL) was added. The solution was placed on an ice bath, and acetylpyridine **3** (5.60 g, 46.2 mmol) was added drop-wise over 10 min while stirring. The reaction was stirred for 20 min at 0°C before an ice-cold solution of $NaHSO_3$ (14.5 g, 139 mmol) in H_2O (100 mL)/MeOH (300 mL) was added. The reaction was allowed to heat to room temperature and kept stirring overnight. MeOH was removed under reduced pressure, H_2O (50 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were washed with HCl (1*M*, 50 mL), $NaHCO_3$ (sat, 100 mL), and water (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to yield 5.64 g (73%) of the title compound **4** as a slightly yellow solid, pure by NMR.

3-Amino-4-acetylpyridine (5). The title compound **5** was prepared as described in literature [20] from nitropyridine **4** and $Na_2S_2O_4$ in EtOH to afford 69% yield, pure by ^1H NMR; mp 91–92°C (lit. [20], 89–91°C).

4-Acetyl-3-iodopyridine (6). The title compound **6** was prepared by a method described in literature [22]. In a mortar, to amine **5** (100 mg, 0.734 mmol) and water (150 μL) was added *p*-TsOH·H_2O (560 mg, 2.94 mmol). The mixture was ground for 2 min before $NaNO_2$ (152 mg, 2.20 mmol) was added in two portions. The reaction was ground regularly over 10 min with a pestle until TLC showed full conversion of the amine. KI (366 mg, 2.20 mmol) was added, and the grinding was continued for 5 min before minor amounts of water (10 × 100 μL) was added during the next 10 min. Water (3 mL) and then Na_2SO_3 (10%, 10 mL) were added before extraction with EtOAc (3 × 20 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give 140 mg of brown oil. The crude product was purified by flash chromatography (EtOAc/pentane (1:1)) to give 130 mg (72%) of the title compound **6**, as an yellow oil, pure by NMR; R_f 0.40 (EtOAc/pentane (1:1)); IR 1700, 1393, 1356, 1249, 1010, 829, 680, 604, 590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.03 (s, 1H, py-H2), 8.63 (d, J = 4.8 Hz, 1H, py-H6), 7.32 (d, J = 4.8 Hz, 1H, py-H5), 2.62 (s, 3H, CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 200.5 (C=O), 158.9 (py-C2), 151.0 (py-C4), 149.3 (py-C6), 121.9 (py-C5), 89.4 (py-C3), 29.4 (CH_3); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M+H]^+$ C_7H_7INO: 247.9567; obsd 247.9581.

Acknowledgment. Trygve Andreassen, Ph.D., at the NT-faculty NMR centre at NTNU is acknowledged for his NMR technical assistance.

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Corrections to the publisher:

- Abstract: Atoms (NH, NH_2) in picture are unclear/partly missing.
- Introduction: Structure numbers should be bold (IVb, 2, (5), (2), IVb, 1, 4, 5, 1, 2, (2/2')).
- Scheme 2: Top parts of the O's are missing.
- Experimental: 400MHz and 100MHz should be replaced with 400 MHz and 100 MHz (with space) throughout the text.

Paper VIII

Vegar Stockmann and Anne Fiksdahl

Synthesis of Novel 1,7-Naphthyridines by Friedländer Condensation of Pyridine Substrates

J. Heterocyclic Chem. **2010**, accepted.

Synthesis of Novel 1,7-Naphthyridines by Friedländer Condensation of Pyridine Substrates

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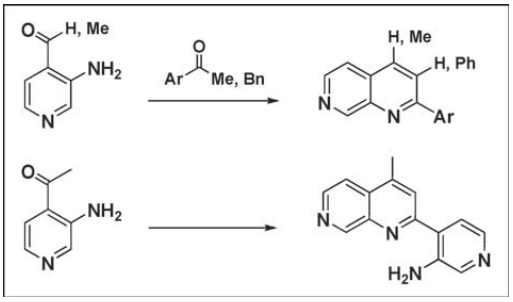
Received June 15, 2010
DOI 10.1002/jhet.657
Published online 00 Month 2010 in Wiley Online Library (wileyonlinelibrary.com).



The general ability of appropriate pyridyl compounds (aldehyde or ketone) to undergo Friedländer condensation to give different 1,7-naphthyridines has been demonstrated. 2,4-Disubstituted 1,7-naphthyridine **8** was prepared from 3-amino-4-acetylpyridine (**6**) and ketone **4** (82%). The Friedländer self-condensation of pyridyl substrate **6** is reported, as well. The dimer product, 2-(3-aminopyridin-4-yl)-4-methyl-1,7-naphthyridine (**7**), was obtained in 97% yield. 2-Aryl- and 2,3-diaryl-1,7-naphthyridines (**16**–**18**) were prepared from 3-aminoisonicotinaldehyde (**13**) and arylketones **4**, **14**, and **15** (28–71%). The key substrates **6** and **13** are readily available via the improved pyridine nitration method.

J. Heterocyclic Chem., **00**, 00 (2010).

INTRODUCTION

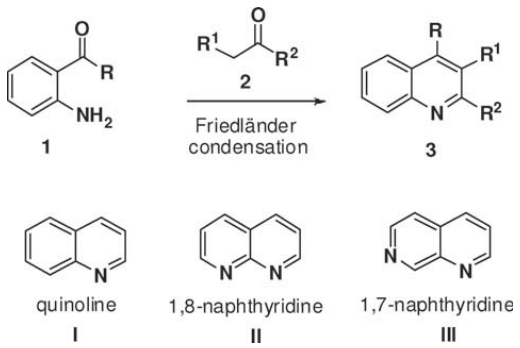
The Friedländer reaction is a cyclisation method consisting of (i) a base- or acid-promoted aldol condensation of an aromatic 2-amino-substituted carbonyl compound **1**, with an appropriate ketone **2**, possessing a reactive a-CH_2 group and (ii) an amine-carbonyl cyclo- S1 dehydration to form an imine moiety (Scheme 1). The Friedländer annulations are often carried out by refluxing an ethanolic solution of the reactants in the presence of NaOH. This cyclocondensation method is widely used in heterocyclic chemistry, in particular, for the preparation of substituted quinolines **3**. Recent advances in the Friedländer reaction [1], as well as the Friedländer approach for quinoline synthesis [2] have been reviewed. New protocols for the preparation of quinoline derivatives by Friedländer annulation reactions have lately been reported [3–7].

The classical Friedländer reaction conditions make use of 2-aminobenzaldehyde (**1**, *R*=*H*) to afford quinolines, **I**, **3** (Scheme 1). However, in recent years, the substrate has been replaced with 2-amino-nicotinaldehyde, allowing the preparation of some 1,8-naphthyridines, **II** [5,8–14]. Naphthyridines provide an important scaffold for a variety of compounds of unique biological activities. Their synthesis, properties, reactivity and biological activity are covered in several reviews [15–17]. The synthetic use of the Friedländer reaction for preparation of 1,7-naphthyridines (**III**) has, however, been limited by the inconvenient preparation methods for the necessary 2-amino carbonyl compounds, such as 3-aminoisonicotinaldehyde (**13**) [18]. Therefore, the Friedländer approach has nearly not been applied for the preparation of 1,7-naphthyridines [19] and the biological activity of 1,7-naphthyridines has been less studied. 1,7-Naphthyridines are, however, reported to be more active than the corresponding 1,8-isomers as potential new therapeutic antitumor agents [20]. Recently, 1,7-naphthyridine derivatives have been identified as selective Tpl2 kinase inhibitors. Tpl2 is an attractive target for the treatment of rheumatoid arthritis [21].

Based on the fact that a number of substituted 3-nitropyridines have become readily available through an improved nitration method [22,23], we have readily access to appropriate *o*-amino-4-carbonylpyridine substrates, such as 3-amino-4-acetylpyridine (**6**, Scheme 2) S2 and 3-amino-4-pyridinecarboxaldehyde (**13**, Scheme 3), S3 for the preparation of 1,7-naphthyridines. The present results on 1,7-naphthyridine syntheses are part of an

ED1

Scheme 1. • • •.



investigation of the chemistry of nitropyridines, which is in progress in our laboratories.

RESULTS AND DISCUSSION

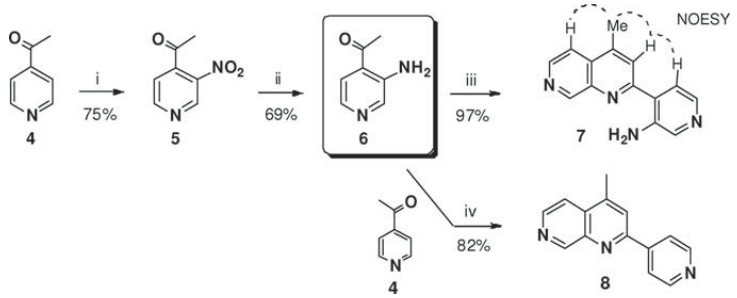
3-Amino-4-acetylpyridine (**6**) was prepared by nitration and reduction (Scheme 2) [24]. The dual functionality of aminopyridylketone **6** enables an internal Friedländer self-condensation. In fact, substrate **6** underwent a Friedländer dimerisation reaction by treatment of excess (1.5 equiv) NaH in dry THF at 0–20°C in 2 h. The 1,7-naphthyridine product **7** was obtained in quantitative yield, which is exceptional compared to the highest yields (80–90%) normally reported for the Friedländer reaction [1]. The structure was unambiguously confirmed by HMBC and HSQC experiments. NOESY experiments of product **7** showed a through-space proximity between H_3 and both C_4—CH_3 and pyridine-H_5 as well as between C_4—CH_3 and H_5.

Aminoketones are less frequently used in the Friedländer reactions than aminoaldehydes, since the self-condensation, as discussed above, may represent a problem and therefore limit the scope and generality of the reaction. Therefore, the capability of 3-amino-4-acetylpyridine (**6**) to undergo regular Friedländer condensation with other ketones and, thus, to exclude dimerisation, was studied. Indeed, treatment of methylpyridylketone **4** with NaH in THF and subsequent addition of substrate **6**, afforded the 2,4-disubstituted 1,7-naphthyridine **8**. The ratio between the desired product **8** and the dimer product **7** increased by reducing the amount of NaH from 2.5 to 1.1 equivalent. Rising the initial reaction temperature from 0 to 20°C to assure full deprotonation of ketone **4** before the addition of substrate **6**, increased the yield of the target product **8** twofold. As a result, the optimized reaction conditions allowed the isolation of 1,7-naphthyridine **8** in 82% yield.

3-Aminoisonicotinaldehyde (**13**) was also used as a substrate to demonstrate the general potential of pyridyl compounds for the preparation of 1,7-naphthyridines by the Friedländer condensation (Scheme 3). Methyl 3-aminoisonicotinate (**11**), readily accessible from methyl isonicotinate (**9**) by nitration and reduction [24], was transformed into the corresponding Weinreb amide (**12**, 73%), using the Me_2AlCl/MeONHMe·HCl reagent system [25]. Following reduction with $LiAlH_4$ afforded 3-aminoisonicotinaldehyde (**13**, 90%).

Friedländer reactions of pyridyl substrate **13** with the respective ketones **4**, **14**, and **15** and 2–2.5 equiv NaH in THF gave the 2-aryl and 2,3-diaryl-1,7-naphthyridines **16–18**. Ketone **15** was prepared from isonicotinaldehyde via 4-dimethoxymethylpyridine, BuLi proton abstraction, subsequent nucleophilic substitution of benzylchloride and hydrolysis [26]. Ketones **4** and **14** were commercially available. Product **16** has previously been prepared by standard Friedländer reaction conditions (NaOH/EtOH) in lower yield (60%) [19] than obtained by our alternative NaH/THF method (71%). The novel products **17** and **18** were obtained in 28–31% yield, due to the formation of unidentified by-products. The yields of products **16–18** were not influenced by the order of reactant addition. HMBC and HSQC data obtained by

Scheme 2. Reagents and conditions: (i) 1. N_2O_5 in $MeNO_2$, 0°C and 2. $NaHSO_3$ in MeOH/H_2O; (ii) $Na_2S_2O_4$ in EtOH, reflux, 6 h; (iii) NaH, THF 0°C → rt, 2 h; (iv) NaH, THF, rt, 2 h.



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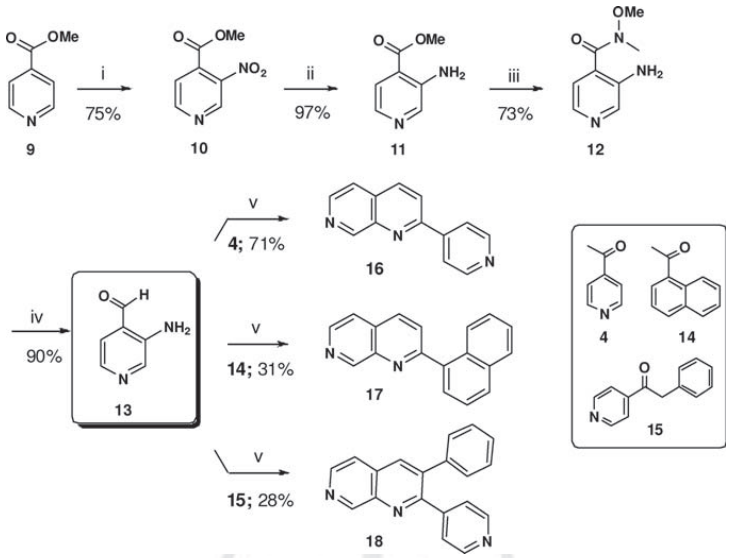
Scheme 3. Reagents and conditions: (i) 1. N_2O_5 in $MeNO_2$, 0°C and 2. $NaHSO_3$ in $MeOH/H_2O$; (ii) $Na_2S_2O_4$ in EtOH, reflux, 6 h; (iii) MeONHMe·HCl/Me_2AlCl in DCM, rt, 20 h; (iv) $LiAlH_4$ in THF, −15°C; (v) NaH in THF, 0°C → rt, 2 h.



2D NMR experiments of products **16**–**18** confirmed the respective structures.

CONCLUSION

Optimized reaction conditions allowed Friedländer cyclocondensation of substrate **6** and methylpyridylketone **4** to afford 2,4-disubstituted 1,7-naphthyridine **8** (82%). 3-Amino-4-acetylpyridine (**6**) underwent a Friedländer self-condensation by treatment of excess NaH to afford the 1,7-naphthyridine product **7** in quantitative yield. 3-Aminoisonicotinaldehyde (**13**) reacted by Friedländer condensation with arylketones **4**, **14**, and **15** to give 2-aryl- and 2,3-diaryl-1,7-naphthyridines **16**–**18** (28–71%). Substrates **6** and **13** were readily obtained by pyridine nitration and reduction. Thus, the present results demonstrate that the pyridine nitration pathway followed by Friedländer condensation represent a convenient strategy for the preparation of 1,7-naphthyridines.

EXPERIMENTAL

General. Chemicals: NaH, $LiAlH_4$, MeONHMe·HCl, Me_2AlCl (Aldrich), 4-acetylpyridine (**4**, Fluka), 1-acetonaphthone (**14**, Aldrich). 3-Amino-4-acetylpyridine (**6**) [24], methyl 3-aminoisonicotinate (**11**) [24], and 2-phenyl-1-(pyridine-4-yl)ethanone (**15**) [26] were prepared as described in literature. Solvents: *pro analysi* quality. Dry THF and DCM were collected from a MB SPS-800 solvent purification system. All reactions were performed under argon atmosphere in predried glassware. NMR: Bruker Avance DPX 400 MHz. ^1H and ^{13}C chemical shifts are reported in ppm downfield from TMS. J values are given in Hz. ESI-MS accurate mass determination was performed on a Waters QTOF II instrument. IR: Nicolet 20SXC FT-IR spectrophotometer. IR spectra were recorded using a Smart Endurance reflexion cell, unless KBr are specified. All melting points are uncorrected and were recorded on a Stuart apparatus. Flash chromatography: SiO_2 (SDS, 60 Å, 40–63 μm).

2-(3-Aminopyridin-4-yl)-4-methyl-1,7-naphthyridine (7). A solution of amine **6** (113 mg, 0.830 mmol) in dry THF (3 mL) was added dropwise over 10 min to a solution of NaH (30.0 mg, 1.25 mmol) in dry THF (2 mL) at 0°C and kept stirring for 15 min. The reaction was allowed to heat to room temperature and stirred for 2 h before quenching with water (15 mL). The mixture was extracted with EtOAc (4 × 20 mL) and the combined organic phases were dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash column chromatography (gradient; 5–10% $MeOH/CH_2Cl_2$) to give 95 mg (97%) of the title compound **7** as a yellow solid, mp 250–251°C, pure by NMR; R_f 0.35 (10% $MeOH/CH_2Cl_2$); IR (KBr): 3348, 3244, 3123, 1602, 1561, 1503, 1434, 1240, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d_H 9.47 (d, J = 0.8 Hz, 1H, H8), 8.67 (d, J = 5.6 Hz, 1H, H6), 8.27 (s, 1H, py'—H2), 8.07 (d, J = 5.2 Hz, 1H, py'—H6), 7.93 (s, 1H, H3), 7.80 (dd, J = 5.6, 0.8 Hz, 1H, H5), 7.55 (d, J = 5.2 Hz, 1H, py'—H5), 6.31 (br s, 2H, —NH_2), 2.78 (s, 3H, C4—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): d_C 158.2 (C2), 153.9 (C8), 144.8 (C4), 144.2 (C6), 142.9 (py'—C3), 141.7 (C8a), 140.9 (py'—C2), 138.3 (py'—C6), 130.2 (C4a), 124.9 (py'—C4), 123.6 (C3), 121.9 (py'—C5), 116.3 (C5), 18.5 (C4—CH_3); NMR assignments are based on HMBC, HSQC, and NOESY experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_{14}H_{13}N_4$:

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237.1135; obsd 237.1151; calcd for $[M + Na]^+$ $C_{14}H_{12}N_4Na$: 259.0954; obsd 259.0962.

4-Methyl-2-(pyridin-4-yl)-1,7-naphthyridine (8). To a solution of NaH (18.0 mg, 0.750 mmol) in dry THF (2 mL) at 0°C was added ketone **4** (100 mg, 0.825 mmol). The reaction was stirred for 15 min at 0°C and then 15 min at room temperature. Amine **6** (94.0 mg, 0.690 mmol) in THF (1 mL) was added dropwise over 15 min and the reaction was stirred for 2 h at room temperature. The reaction mixture was diluted with THF (1 mL) before it was added to water (20 mL). After extraction with EtOAc (3 × 20 mL), drying over $NaSO_4$ and concentration under reduced pressure, the crude product was purified by flash chromatography (gradient: 5–10% MeOH/CH_2Cl_2) to give 126 mg (82%) of the title compound **8** as a white solid, mp 135–136°C, pure by NMR. Compound **7** was isolated as a by-product (8 mg, 10%). **8**: R_f 0.15 (5% MeOH/CH_2Cl_2); IR: 1595, 1417, 837, 829, 750, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d_H 9.57 (s, 1H, H8), 8.81 (d, J = 5.6 Hz, 2H, py'—H2, —H6), 8.67 (d, J = 5.6 Hz, 1H, H6), 8.06 (d, J = 5.6 Hz, 2H, py'—H3, —H5), 7.92 (s, 1H, H3), 7.79 (d, J = 5.6 Hz, 1H, H5), 2.79 (s, 3H, C4—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): d_C 155.9 (C2), 155.4 (C8), 150.8 (py'—C2, —C6), 146.0 (py'—C4), 145.2 (C4), 144.3 (C6), 143.2 (C8a), 131.2 (C4a), 122.7 (C3), 121.7 (py'—C3, —C5), 116.4 (C5), 18.6 (C4—CH_3); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_{14}H_{12}N_3$: 222.1026; obsd 222.1029.

3-Amino-*N*-methoxy-*N*-methylisonicotinamide (12). To a solution of MeONHMe·HCl (2.00 g, 20.5 mmol) in dry CH_2Cl_2 (50 mL) at 0°C was added Me_2AlCl (1 *M* in hexanes, 20.5 mL, 20.5 mmol) dropwise over 30 min. The reaction was allowed to heat to room temperature over 2 h. A solution of amine **11** (1.265 g, 8.21 mmol) in dry CH_2Cl_2 (50 mL) was added and the reaction was stirred for 20 h. A solution of borate buffer (pH 8.0, 80 mL) was added and stirring was continued for 10 min. Extraction with CH_2Cl_2 (4 × 60 mL), drying over Na_2SO_4, concentration under reduced pressure and flash chromatography (gradient: 5–10% MeOH/CH_2Cl_2) afforded the title compound **12** as a white solid, 1.09 g (73%), mp 94–95°C, pure by NMR; R_f 0.17 (5% MeOH/CH_2Cl_2); IR: 3449, 3310, 3141, 1623, 1583, 1418, 1384, 983, 968, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d_H 8.18 (s, 1H, py—H2), 7.98 (d, J = 4.8 Hz, 1H, py—H6), 7.25 (d, J = 4.8 Hz, 1H, py—H5), 4.64 (br s, 2H, NH_2), 3.57 (s, 3H, —OCH_3), 3.37 (s, 3H, —CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): d_C 167.5 (C=O), 141.7 (py—C3), 139.8 (py—C2), 138.2 (py—C6), 123.0 (py—C4), 121.8 (py—C5), 61.5 (O—CH_3), 33.3 (N—CH_3); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_8H_{12}N_3O_2$: 182.0924; obsd 182.0931.

3-Aminoisonicotinaldehyde (13). A solution of Weinreb amide **12** (138 mg, 0.759 mmol) in dry THF (2 mL) was added dropwise over 15 min to a solution of $LiAlH_4$ (86.4 mg, 2.28 mmol) in dry THF (3 mL) at −15°C. The reaction was stirred for 1.5 h at −15°C and quenched by pouring the mixture into a phosphate buffer solution (1 *M*, pH 7.5, 30 mL) at 0°C. The aqueous solution was extracted with ether (3 × 20 mL), dried over Na_2SO_4 and concentrated to give the title compound **13** as a yellow solid, 83 mg (90%), pure by ^1H NMR; ^1H NMR (400 MHz, $CDCl_3$): d_H 9.97 (s, 1H, —CHO), 8.24 (s, 1H, py—H2), 8.07 (d, J = 5.2 Hz, 1H, py—H6), 7.33 (d, J = 5.2 Hz, 1H, py—H5), 6.00 (br s, 2H, NH_2).

General procedure for the formation of the 1,7-naphthyridines 16–18. 3-Aminoisonicotinaldehyde (**13**) in dry THF (1 mL) was added to a solution NaH in dry THF (1 mL) at 0°C. The appropriate ketone **4**, **14**, or **15** in dry THF (2 mL) was added dropwise over 10 min. The reaction was stirred for 15 min at 0°C before it was allowed to heat to room temperature and stirred for 2 h. Water (15 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The products **16–18** were isolated after purification by flash column chromatography.

2-(Pyridin-4-yl)-1,7-naphthyridine (16). The title compound was prepared form aminoaldehyde **13** (34.0 mg, 0.278 mmol), ketone **4** (37.0 mg, 0.305 mmol) and NaH (15.0 mg, 0.625 mmol) [19]. After flash column chromatography (gradient: 5–10% MeOH/CH_2Cl_2), product **16** was isolated as a white solid, 41 mg (71%), mp 157–158°C, pure by NMR; R_f 0.45 (10% MeOH/CH_2Cl_2); IR (KBr): 3039, 1596, 1489, 1420, 948, 828, 788, 705, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d_H 9.61 (s, 1H, H8), 8.82 (dd, J = 4.8, 1.6 Hz, 2H, py'—H2, —H6), 8.66 (d, J = 5.6 Hz, 1H, H6), 8.30 (d, J = 8.4 Hz, 1H, H4), 8.11 (d, J = 8.4 Hz, 1H, H3), 8.08 (dd, J = 4.8, 1.6 Hz, 2H, py'—H3, —H5), 7.70 (d, J = 5.6 Hz, 1H, H5); ^{13}C NMR (100 MHz, $CDCl_3$): d_C 156.3 (C2), 154.9 (C8), 150.9 (py'—C2, —C6), 145.7 (py'—C4), 144.4 (C6), 143.4 (C8a), 136.2 (C4), 130.7 (C4a), 122.6 (C3), 121.6 (py'—C3, —C5), 119.7 (C5); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_{13}H_{10}N_3$: 208.0869; obsd 208.0880; calcd for $[M + Na]^+$ $C_{13}H_9N_3Na$: 230.0689; obsd 230.0691. AQ1

2-(Naphthalen-1-yl)-1,7-naphthyridine (17). The title compound was prepared form aminoaldehyde **13** (29.0 mg, 0.237 mmol), ketone **14** (42.0 mg, 0.247 mmol), and NaH (15.0 mg, 0.625 mmol). After flash column chromatography [EtOAc/pentane (1:1)], product **17** was isolated as a white solid, 19 mg (31%), mp 116–117°C, pure by NMR; R_f 0.27 [EtOAc/pentane (1:1)]; IR: 3045, 1598, 1496, 1409, 1241, 942, 855, 803, 789, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d_H 9.64 (s, 1H, H8), 8.69 (d, J = 5.6 Hz, 1H, H6), 8.28 (d, J = 8.4 Hz, 1H, H4), 8.12 (m, 1H, Np'—H), 7.97 (m, 2H, Np'—H), 7.92 (d, J = 8.4 Hz, 1H, H3), 7.74 (d, J = 5.6 Hz, 1H, H5), 7.72 (m, 1H, Np'—H), 7.62 (m, 1H, Np'—H) 7.52 (m, 2H, Np'—H); ^{13}C NMR (100 MHz, $CDCl_3$): d_C 161.4 (C2), 154.7 (C8), 144.1 (C6), 143.4 (C8a), 138.0 (Np'—C_q), 135.1 (C4), 134.2 (Np'—C_q), 131.2 (Np'—C_q), 130.1 (C4a), 129.9 (Np'—C), 128.8 (Np'—C), 128.3 (Np'—C), 127.5 (C3), 127.1 (Np'—C), 126.4 (Np'—C), 125.6 (Np'—C), 125.5 (Np'—C), 119.9 (C5); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_{18}H_{13}N_2$: 257.1073; obsd 257.1082.

3-Phenyl-2-(pyridin-4-yl)-1,7-naphthyridine (18). The title compound was prepared form aminoaldehyde **13** (47.0 mg, 0.385 mmol), ketone **15** (82 mg, 0.416 mmol) and NaH (19.0 mg, 0.792 mmol). After flash column chromatography (gradient: 5–10% MeOH/CH_2Cl_2), product **18** was isolated as an orange solid, 30 mg (28%), mp 131-132°C, pure by NMR; R_f 0.16 (5% MeOH/CH_2Cl_2); IR (KBr): 3030, 1598, 1586, 1408, 970, 909, 831, 819, 767, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d_H 9.61 (s, 1H, H8), 8.68 (d, J = 5.6 Hz, 1H, H6), 8.57 (d, J = 6.0 Hz, 2H, py'—H2, —H6), 8.21 (s, 1H, H4), 7.72 (d, J = 5.6 Hz, 1H, H5), 7.36 (m, 5H, py'—H3, —H5,

Ph—H3, —H4, —H5), 7.25 (m, 2H, Ph—H2, —H6); ^{13}C NMR (100 MHz, $CDCl_3$): d_C 157.6 (C2), 154.6 (C8), 149.9 (py'—C2, —C6), 147.3 (py'—C4), 144.7 (C6), 142.4 (C8a), 138.7 (C3), 138.3 (Ph—C1), 136.6 (C4), 130.5 (C4a), 129.7 (Ph—C2, —C6), 128.9 (Ph—C3, —C5), 128.6 (Ph—C4) 124.5 (py'—C3, —C5), 119.7 (C5); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd for $[M + H]^+$ $C_{19}H_{14}N_3$: 284.1182; obsd 284.1185; calcd for $[M + Na]^+$ $C_{19}H_{13}N_3Na$: 307.1032; obsd 307.1032.

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Corrections to the publisher:

- Greek letters: a-CH_2, d_H and d_C should be replaced with α-CH_2, δ_H and δ_C.
- $(\mathbf{1},\ R{=}H)$: Correct to (**1**, R = H).
- No titles in schemes. Reduce size of Scheme 1. Move text in Scheme 1 and 2 to below the picture.
- Experimental, General: Italic J.
- All hyphens in the experimental part should be shorter.

Paper IX

Vegar Stockmann, Svein Jacob Kaspersen, Alexander Nicolaisen and Anne Fiksdahl

Studies on reactive pyridylketones formed by Weinreb transformations

J. Heterocyclic Chem. **2010**, submitted.

Studies on reactive pyridylketones formed by Weinreb transformations

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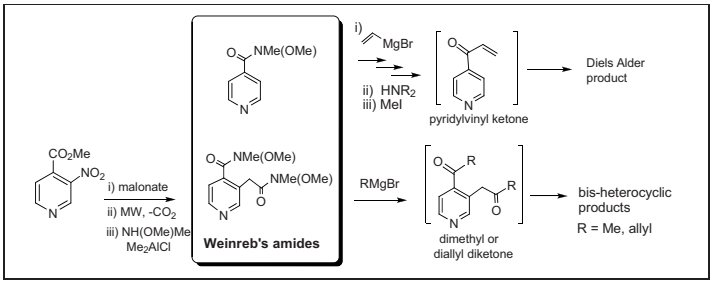


Abstract: A method has been developed in order to allow the preparation of reactive pure vinylpyridylketones and activated vinylketones, in general, to be used in further reactions, such as cycloadditions. The process is based on the Weinreb's amide transformation and includes a quarternary ammonium intermediate and subsequent elimination. Additionally, based on our previous results on the malonate alkylation of 3-nitropyridines and subsequent synthetic applications, we present the studies on the transformation of pyridyl malonate derivative **3** via the Weinreb's amide **4** and reactive methylpyridyl- (**17**) and allylpyridylketone (**6**) into bis-heterocyclic products **18**, **19** and **8**, **20**, **21**, respectively.

J. Heterocyclic Chem. (2010)

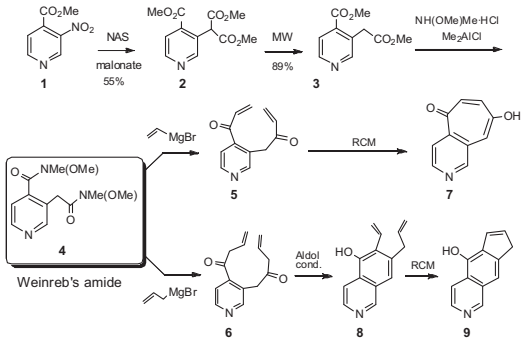
INTRODUCTION

Aromatic alkylation methods are essential in organic synthesis since more complex carbon skeletons can be constructed. We have previously reported the nucleophilic aromatic substitution (NAS) [1-3] of the nitro group in 3-nitropyridyl carboxylate (**1**) with malonate (Scheme 1). The versatility of the 3-pyridylmalonate product **2** was demonstrated by subsequent transformations to give new fused bis-heterocycles.

The initial target of the present project was the preparation of the two potentially biological active pyridoisotropolone analogue **7** and cyclopenta[g]isoquinolinol **9** from pyridyl malonate **2** (Scheme 1). Tropolones are widespread natural products with a broad range of anti-bacterial, -fungal, -tumour and insecticide effects [4,5], while cyclopentaisoquinoline compounds, similar to product **9**, have been prepared as cancer chemotherapeutic agents [6-9]. The acidity and properties of the cyclopentadienide ion of similar cyclopentaphenanthrenes have been studied [10-12]. Thus, derivatives of compound **9** would show pronounced acidity due to the strong anionic stabilising resonance effect and the electron-withdrawing pyridine moiety.

Our approach for the preparation of the 7-membered cyclic products **7** and the tricyclic product **9** was based on RCM of the vinyl-vinyl and vinyl-allyl moieties of compounds **5** and **8**, prepared from pyridyl malonate (**2**) via diester **3**, Weinreb's amide **4** and subsequent Weinreb ketone transformations (Scheme 1) [13,14]. 7-Allyl-6-vinylisoquinolinolol **8** would be obtained by an intramolecular regioselective aldol cyclisation of diallylketone **6**.

Scheme 1



However, some challenging effects were observed by the transformation of Weinreb's amide **4** into the reactive divinyl- and diallylketones **5** and **6**. Further investigations were needed to identify the formed products and preferably establish suitable methods for the handling and application of such reactive pyridyl ketones. The results of the studies are discussed below.

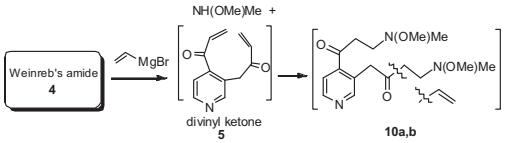
RESULTS AND DISCUSSION

Weinreb's amides, *N*-methoxy-*N*-methyl amides, formed by ester aminolysis [15], are useful intermediates in organic synthesis, since they react efficiently with organometallic agents, such as Grignard reagents, to selectively produce ketones. A corresponding two-step procedure allowed a direct allylation of carboxylic acids. [16]. We applied a more efficient process, utilising the modified Me_2AlCl/MeONHMe·HCl reagent system [17] for the preparation of Weinreb's amide **4** (74%) from homochinchomeric acid dimethyl ester **3**, readily obtained (89%) by microwave (MW) promoted mono-decarboxylation of pyridyl malonate **2** (Scheme 1) [3].

i) Vinylpyridylketone

The ketone transformation of Weinreb's amide **4** into divinylketone (**5**) intermediate for the preparation of pyridoisotropolone **7** (Scheme 1) did not take place. The reaction resulted in a tarry and hardly soluble material, and no products were isolated or identified. The highly reactive vinylpyridylketone **5** may react in several ways. Due to pyridyl activation, instant mono or double Michael additions of present potential nucleophiles, such as the amine leaving group, NHMe(OMe), to the vinylketone groups of **5** would lead to a mixture of unwanted intermediates and products. Compounds, such as **10a** or **10b**, were not observed, but illustrate the potential reactivity of vinylpyridylketone **5** (Scheme 2). The direct synthesis of such β-aminoketones from Weinreb's amides *via* sequential nucleophilic vinyl substitution and Michael reaction is well known [18,19].

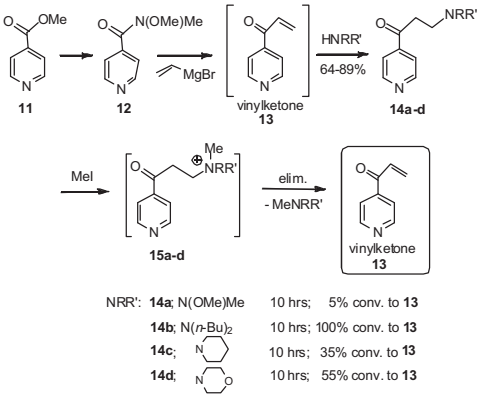
Scheme 2



In order to develop a practical and selective preparation method for reactive vinylpyridylketones and activated vinylketones in general, the transformations of Weinreb's amide **12**, obtained from methyl isonicotinate (**11**, Scheme 3), was studied. By the conversion of intermediate **12** with vinylMgBr, the formed vinylketone **13** was directly trapped *in situ* by the present amine leaving group and the corresponding -N(OMe)Me Michael product (**14a**) was isolated (70%).

Furthermore, the corresponding amine products **14b-d** (64-89%) were formed by *in situ* trapping of the vinylketone **13** with respectively dibutylamine, piperidine or morpholine, added to the reaction mixture. To enable the formation of a stable and pure solution of the reactive vinylpyridylketone **13**, the isolated amine products **14a-d** were converted into quarternary ammonium intermediates (**15a-d**) by reaction with methyl iodide (Scheme 3). *In situ* amine elimination afforded the desired vinylketone **13**. The dibutylamine intermediate **14b** gave full conversion to the vinylketone **13** in 10 hrs, as shown by nmr of the reaction mixture. A solution of vinylketone **13** in $CDCl_3$ (61%, Scheme 4), pure by ^{1}H nmr, was obtained after repeated washing with water and final argon-flush to remove excess MeI. The yield was determined by ^{1}H nmr with 1,2,4,5-tetrachlorobenzene as an internal standard. Low to moderate conversion (5-55%) of amines **14a**,**c**,**d** into vinylketone **13** was obtained through their respective quarternary ammonium compounds **15a**,**c**,**d**.

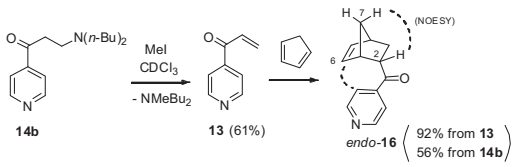
Scheme 3



To demonstrate the utility of the reactive vinylpyridylketone **13** in subsequent synthetic transformations, the stable and pure solution of vinylketone **13** was treated with cyclopentadiene to undergo a Diels-Alder cycloaddition (Scheme 4). The bicyclo[2.2.1]heptenyl product **16** was isolated in excellent yield (92% from vinylketone **13**; 56% from amine **14b**). The *endo* isomer was exclusively formed, as

confirmed by 2D nmr, since NOESY effects between H2 and H7, and between pyridine-H3/-H5 and H6, were observed, excluding the *exo* product. No traces of the *exo*-isomer could be observed.

Scheme 4



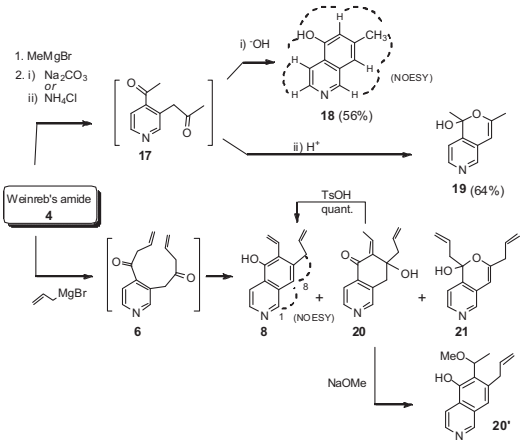
The developed method was not successful for the generation of divinylketone **5** from Weinreb's amide **4**, probably due to competing cyclisation reactions, as discussed below for allylpyridylketone **6**.

ii) Allylpyridylketone

The transformation of Weinreb's amide **4** with allylmagnesium bromide (Scheme 5) gave a mixture of cyclisation products *via* the initially formed diallylketone (**6**). In order to identify these new heterocyclic compounds, the MeMgBr conversion of amide **4** and, hence, the formation of dimethyldiketone intermediate **17** (Scheme 5) was chosen as a less complex reaction to study the Grignard transformations of Weinreb's amide **4**. The formed cyclic products were dependant on the work-up procedures. The MeMgBr conversion of amide **4** afforded the isoquinolinol product **18** (56%), formed by regioselective intramolecular aldol condensation of diketone **17**, by quenching the reaction with water and subsequent alkalic treatment of the crude product. The hemiketal **19** (64%), formed by O-acylation of diketone **17**, was obtained as the main product after NH_4Cl work-up. Such cyclocondensations are well known from the preparation of 2*H*- and 4*H*-pyran natural product from 1,5-diketone precursors [20-22].

The reaction of Weinreb's amide **4** with allylMgBr gave a crude mixture mainly affording isoquinolinol **8** (13%), analogues to compound **18** discussed above, and the corresponding aldol precursor, the ethylidene compound **20**, by adding NaOH (5M) to the solution and thus extraction from an alkalic solution. Product **8** (11%) was also obtained by quenching with an NH_4Cl solution and final extraction. The aldol precursor compound **20** (26%), and minor amounts of the hemiketal **21** (6%), similar to product **19** above, were isolated as well. The hemiketal **21** was later isolated in higher yield (21%) by quenching with an ice-cold solution of NH_4Cl. The conjugated addition of a methoxy group to the exocyclic double bond in product **20**, giving methoxy-product **20'**, confirmed the keto-ethylidene structure of **20**. Separate experiments showed that aromatisation and ethylidene-vinyl isomerisation and, hence, full conversion of **20** into **8** could be performed by treatment of **20** in $CDCl_3$ with *p*-TsOH in 10 hours. Alternative treatments with HCl (1-5M) or NaOH (3-5M) were not successful, mainly affording the elimination product without any ethylidene-vinyl isomerisation. We were, however, not able to develop optimised conditions allowing direct conversion of Weinreb's amide **4** into the desired compound **8** as the major product.

Scheme 5



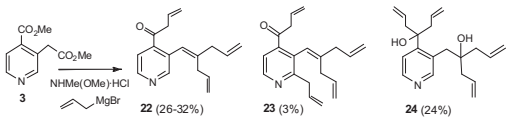
The identity of the vinyl-allyl-isoquinolinol product **8** was confirmed by HMBC, HSQC and NOESY nmr experiments. In particular, the NOESY results supported the regioselective aldol reaction and structure **8**, since a through-space proximity of H8 with both H1 and the allylic CH_2 group was observed. The isolation of small amounts of compound **8** was laborious, and the compound was never isolated in sufficient amounts to permit a final RCM for the preparation of **9** (Scheme 1).

The conclusive structure elucidations of isoquinolinol **8** and the cyclic diallylhemiketal **21** were based on comparative studies of the fully characterised products **18** and **19**, respectively. In particular, the unambiguous ^{13}C nmr data correlations in pairs between **8**/**18** and **19**/**21** were significant.

Attempts to develop a one-pot procedure for the formation of allyl-vinyl-isoquinolinol **8**, applying allyl-MgCl both to generate the Me(MeO)NMgCl reagent [15]

and to convert the formed Weinreb's amide **4** into di-allyl product **6**, were unsuccessful. Polyallylation of the most reactive carbonyl group mainly took place (**22** and **24**, 24-32%, Scheme 6). Minor amount of the oxidative nucleophilic substitution product **23** was also observed. [23].

Scheme 6



CONCLUSION

A method was developed to enable the preparation of reactive pure vinylpyridylketones (e.g. **13**) from Weinreb's amides (e.g. **4**), including formation of a b-aminoketone (e.g. **14a-d**), quarternary ammonium intermediates (e.g. **15a-d**) and subsequent elimination. The utility of the reactive vinylketone **13** in further synthesis was demonstrated by the application in Diels-Alder cycloaddition with cyclopentadiene to give the *endo*-bicyclo[2.2.1]heptenyl product (**16**, 92 % from **13**).

The transformation of pyridyl malonate derivative **2** *via* diester **3**, Weinreb's amide **4** and the reactive allylpyridylketone intermediate **6** into cyclisation products was studied. The *in situ* formation of the cyclic aldol products **8** and **20** and the O-acylation hemiketal pyrano-compound **21** from diallylketone **6** took place. The analogous dimethyldiketone **17** formed, correspondingly, hemiketal **19** and the aldol cyclisation product **18**, essential for the structure elucidation of the analogous products **8** and **21**.

EXPERIMENTAL

General. Solvents: *pro analysi* quality. Dry solvents were collected from a MB SPS-800 solvent purification system. All air and moisture sensitive reactions were performed under argon atmosphere in pre-dried glassware. nmr: Bruker Avance DPX 300 and 400 MHz spectrometers. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from TMS. *J* values are given in Hz. ms: Finnigan MAT 95 XL (ei/70 eV). esi-ms accurate mass determination was performed on a waters QTOF II instrument. ir: Nicolet 20SXC FT-IR spectrophotometer. ir spectra were recorded using a Smart Endurance reflexion cell, unless KBr or film are specified. All melting points are uncorrected and were recorded on a Stuart apparatus. Flash chromatography: SiO_2 (sds, 60 Å, 40-63 μm). Dimethyl homochinchomeric acid diester (**3**) was prepared from methyl 3-nitro-4-pyridinecarboxylate (**1**) according to the literature [3].

***N*-methoxy-3-(2-(methoxy(methyl)amino)-2-oxoethyl)-*N*-methylisonicotinamide (Weinreb's amide 4).** MeONHMe·HCl (2.30 g, 23.6 mmol) in CH_2Cl_2 (80 mL) was cooled to 0 °C and added Me_2AlCl (23.6 mL, 23.6 mmol, 1M in hexanes) dropwise. The mixture was stirred for 1.5 h before it was allowed to warm to room temperature. The diester **3** (990 mg, 4.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 8 h, and then quenched with a borate buffer (pH 8, 100 mL). After extraction with CH_2Cl_2 (3 × 60 mL), drying over Na_2SO_4, evaporation of solvent and flash chromatography (5% MeOH/CH_2Cl_2), the title compound **4** was obtained as a transparent oil, 938 mg (74%), pure by ^{1}H nmr; ir (film): 3535, 2972, 2938, 1672, 1592, 1493, 1419, 1385, 1177, 998, 844 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$):δ_H 8.55 (s, 1H, H2), 8.52 (d, *J* = 4.8 Hz, 1H, py-H6), 7.33 (d, *J* = 4.8 Hz, 1H, py-H5), 3.93 (s, 2H, CH_2), 3.77 (s, 3H, CH_2-CO-N-OC$\underline{H}_3$), 3.56 (s, br, 3H, py-CO-N-OC$\underline{H}_3$), 3.26 (s, br, 3H, py-CO-N-C$\underline{H}_3$), 3.14 (s, CH_2-CO-N-C$\underline{H}_3$); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 171.6 (CH_2-$\underline{C}$=O), 168.2 (py-CH2-$\underline{C}$=O), 152.4 (C2), 148.1 (C6), 142.6 (C4), 128.5 (C3), 121.4 (C5), 61.8 / 61.4 (2 × N-OCH_3), 34.0 (CH_2), 32.6 (2 × N-CH_3); nmr assignments are based on HSQC and HMBC experiments; esi-hrms: calcd for $[M+H]^+$ $C_{12}H_{18}N_3O_4$: 268.1297; obsd 268.1293.

N-methoxy-N-methylisonicotinamide (12). The title compound was prepared as described above for Weinreb's amide **4**, using MeONHMe·HCl (1.09 g, 11.2 mmol) in CH_2Cl_2 (80 mL), Me_2AlCl (11.2 ml, 11.2 mmol, 1M in hexanes) and ester **11** (1.02 g, 7.44 mmol) in CH_2Cl_2 (10 mL). Product **12** was obtained after flash chromatography (2.5% CH_2Cl_2/MeOH) as a yellow oil (1.10 g, 89%), pure by NMR; R_f 0.15 (5% MeOH/CH_2Cl_2); ir: 2936w, 1644s, 1405m, 1382m, 980m, 832m, 702m, 630m cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.71 (dd, 2H, *J* = 4.4, 1.6 Hz, H2/H6), 7.52 (dd, 2H, *J* = 4.4, 1.6 Hz, H3/H5), 3.54 (s, 3H, OMe), 3.36 (s, 3H, N-Me), ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 167.5 (C=O), 149.8 (C2, C6), 141.6 (C4), 121.9 (C3, C5), 61.3 (OMe), 33.0 (NMe); nmr assignments are based on HMBC and HSQC experiments esi-hrms: calcd for $[M+H]^+$ $C_8H_{11}N_2O_2$: 167.0815; observed 167.0817.

1-(pyridin-4-yl)prop-2-en-1-one (13). Amine **14b** (40 mg, 0.152 mmol) in $CDCl_3$ (5 mL) was added MeI (95 μL, 1.53 mmol) and stirred for 12 hrs at room temperature. The solution was washed with water (3 × 3 mL) and dried over Na_2SO_4. Argon was bobbled through the solution to remove excess of MeI and the solution was used directly in the next step to form Diels Alder adduct **16**. Quantification was based on 1,2,4,5-tetrachlorobenzene as internal standard; **13** was obtained in 61% yield in a $CDCl_3$ solution, pure by nmr; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.82 (dd, *J* = 4.4, 1.6 Hz, 2H, py-H2/H6); 7.70 (dd, *J*

= 4.4, 1.6 Hz, 2H, py-H3/H5), 7.07 (dd, *J* = 17.2, 10.8 Hz, 1H, CO-CH=), 6.48 (dd, *J* = 17.2, 1.2 Hz, 1H, =C$\underline{H_a}H_b$), 6.01 (dd, *J* = 10.8, 1.2 Hz, 1H, =CH$_a\underline{H_b}$); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 190.5 (C=O), 150.8 (py-C2/C6), 143.3 (py-C4), 132.2 (-CH=), 131.7 (=CH_2), 121.6 (py-C3/C5); nmr assignments are based on HMBC and HSQC experiments; esi-hrms: calcd for $[M+H]^+$ C_8H_8NO 134.0600; observed 134.0602.

***endo*-Bicyclo[2.2.1]hept-5-en-2-yl(pyridin-4-yl)methanone (16).** To the stirred solution of vinylketone **13** in $CDCl_3$ was added freshly distilled cyclopentadiene (100 μL) at -10 °C. The reaction was stirred for 2 h and allowed to warm to room temperature. Evaporation of solvent and flash chromatography (EtOAc/pentane (1:1)) afforded product **16** as a white solid, 17 mg (56% from **14b**, 92% from **13**), mp: 59-60 °C, pure by nmr; R_f 0.30 (EtOAc/pentane (1:1)); ir: 2972w, 1681s, 1411m, 1227m, 1218m, 848s, 717s, 685s, 654s cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.80 (dd, *J* = 4.4, 1.6 Hz, 2H, py-H2/H6), 7.72 (dd, *J* = 4.4, 1.6 Hz, 2H, py-H3/H5), 6.20 (dd, *J* = 5.6, 3.2 Hz, 1H, H5), 5.78 (dd, *J* = 5.6, 2.8 Hz, 1H, H6), 3.79 (app. dt, *J* = 8.8, 4.0 Hz, 1H, H2), 3.25 (app. br s, 1H, H1), 2.99 (app. br s, 1H, H4), 1.98 (ddd, *J* = 11.6, 8.8, 3.6 Hz, 1H, *exo*-H3), 1.62 (ddd, *J* = 11.6, 4.4, 2.4 Hz, 1H, *endo*-H3), 1.50 (m, 2H, H7); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 200.5 (C=O), 151.1 (py-C2/C6), 143.6 (py-C4), 137.9 (C5), 131.6 (C6), 121.5 (py-C3/C5), 50.2 (C7), 48.2 (C2), 47.1 (C1), 43.1 (C4), 29.0 (C3); nmr assignments are based on HSQC, HMBC and NOESY experiments; esi-hrms: calcd for $[M+H]^+$ $C_{13}H_{14}NO$ 200.1070; observed 200.1065.

3-(Methoxy(methyl)amino)-1-(pyridin-4-yl)propan-1-one (14a). A solution of Weinreb's amide **12** (323 mg, 1.94 mmol) in dry THF (15 ml) was added vinylmagnesium bromide (3.89 ml, 3.89 mmol, 1M in THF) dropwise at -78 °C under argon atmosphere. The reaction mixture was stirred for 60 min before it was allowed to warm to room temperature, and stirred for an additional 2 h. Quenching with an NH_4Cl solution (15 ml, sat.), extraction with EtOAc (3 × 50 mL), drying over Na_2SO_4, evaporation of solvent and flash chromatography (5% MeOH/CH_2Cl_2) afforded product **14a** as a light brown oil, 263 mg (70%), pure by nmr; R_f 0.24 (5% MeOH/CH_2Cl_2); ir: 2938w, 1694s, 1408m, 1209m, 1045s, 991m, 787m, 656m; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.82 (dd, *J* = 4.4, 1.6 Hz, 2H, py-H2/H6), 7.74 (dd, *J* = 4.4, 1.6 Hz, 2H, py- H3/H5), 3.45 (s, 3H, OMe), 3.24 (t, *J* = 6.8 Hz, 2H, CO-C$\underline{H_2}$), 3.08 (t, *J* = 6.8 Hz, 2H, C$\underline{H_2}$-N), 2.62 (s, 3H, NMe); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 198.5 (C=O), 150.9 (py-C2/C6), 142.8 (py-C4), 121.0 (py-C3/C5), 59.8 (OMe), 55.2 ($\underline{C}H_2$-N), 45.0 (N-Me), 36.6 (CO-$\underline{C}H_2$); nmr assignments are based on HMBC and HSQC experiments; esi-hrms: calcd for $[M+H]^+$ $C_{10}H_{15}N_2O_2$ 195.1128; observed 195.1126.

3-(Dibutylamino)-1-(pyridin-4-yl)propan-1-one (14b). A stirred solution of Weinreb's amide **12** (400 mg, 2.41 mmol) in dry THF (15 ml) at -78 °C was added vinylmagnesium bromide (3.61 ml, 3.61 mmol, 1M in THF). The reaction was allowed to warm to room temperature and stirred for 1 h. Dibutylamine (4.1 ml, 24 mmol) was added to the mixture, followed by the dropwise addition of H_2O (1 mL) over 10 minutes. Addition of water (50 mL), extraction with diethyl ether (3 × 30 mL), drying over Na_2SO_4, evaporation of solvent and flash chromatography (4% Et_3N in EtOAc/pentane (1:2)) afforded the title compound **14b** as a pale yellow oil, 453 mg (72%), pure by nmr; R_f 0.24 (4% Et_3N in EtOAc/pentane (1:2)); ir: 2955m, 2930m, 1694s, 1407m, 1220w, 773w, 655m; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.81 (dd, *J* = 4.4, 1.6 Hz, 2H, py-H2/H6), 7.72 (dd, *J* = 4.4, 1.6 Hz, 2H, py-H3/H5), 3.10 (t, *J* = 7.6 Hz, 2H, CO-C$\underline{H_2}$), 2.90 (t, *J* = 7.6 Hz, 2H, C$\underline{H_2}$-N), 2.43 (t, *J* = 7.2 Hz, 4H, Bu-H1), 1.39 (m, 4H, Bu-H2), 1.27 (m, 4H, Bu-H3), 0.90 (t, *J* = 7.2 Hz, 6H, Bu-H4); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 199.4 (C=O), 150.9 (py-C2/C6), 142.9 (py-C4), 121.0 (py-C3/C5), 53.8 (Bu-C1), 48.9 ($\underline{C}H_2$-N), 37.0 (CO-$\underline{C}H_2$), 29.2 (Bu-C2), 20.6 (Bu-C3), 14.0 (Bu-C4); nmr assignments are based on HMBC and HSQC experiments; esi-hrms: calcd for $[M+H]^+$ $C_{16}H_{27}N_2O$ 263.2118; observed 263.2114.

3-(Piperidin-1-yl)-1-(pyridin-4-yl)propan-1-one (14c). The title compound was prepared as described above for **14b**, using Weinreb's amide **12** (106.6 mg, 0.641 mmol) in dry THF (5 ml), vinylmagnesium bromide (1.22 ml, 1.22 mmol, 1M in THF) and piperidine (1.21 ml, 12.2 mmol). Flash chromatography (5% MeOH/CH_2Cl_2) afforded the title compound **14c** as a pale brown oil, 124.5 mg (89%), pure by nmr; R_f 0.15 (5% MeOH/CH_2Cl_2); ir (film): 3044w, 2935s, 2852m, 2799m, 1697s, 1555w, 1408s, 735m cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.81 (d, *J* = 4.4, 1.6 Hz, 2H, py-H2/H6); 7.73 (d, *J* = 4.4, 1.6 Hz, 2H, py-H3/H5), 3.18 (t, *J* = 7.2 Hz, 2H, CO-C$\underline{H_2}$), 2.79 (t, *J* = 7.2 Hz, 2H, C$\underline{H_2}$-pip), 2.44 (s, 4H, pip-H2/H6), 1.58 (m, 4H, pip-H3/H5), 1.44 (m, 2H, pip-H4); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 198.9 (C=O), 150.9 (py-C2/C6), 142.8 (py-C4), 121.0 (py-C3/C5), 54,6 (pip-C2/C6), 53.4 ($\underline{C}H_2$-pip), 36.8 (CO-CH_2), 25.9 (pip-C3/C5), 24.2 (pip-C4); nmr assignments are based on HMBC and HSQC experiments; esi-hrms: calcd for $[M+H]^+$ $C_{13}H_{19}N_2O$: 219.1492; observed 219.1495.

3-(Morpholino)-1-(pyridin-4-yl)propan-1-one (14d). The title compound was prepared as described above for **14b**, using Weinreb's amide **12** (240 mg, 1.45 mmol) in dry THF (10 ml), vinylmagnesiumbromide (2.12 ml, 2.17 mmol, 1M in THF) and morpholine (1.26 mL, 14.5 mmol). After flash chromatography (10% MeOH/CH_2Cl_2) the title compound **14d** was obtained as a yellow oil, 229.3 mg (72%), pure by nmr; R_f 0.30 (10% MeOH/CH_2Cl_2); ir: 2953w, 2852w, 1694s, 1408m, 1114s, 988m, 870m, 769m, 663m cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.82 (dd, *J* = 4.4, 1.6 Hz, 2H, py-H2/H6); 7.72 (dd, *J* = 4.4, 1.6 Hz, 2H, py-H3/H5), 3.70 (t, *J* = 4.4 Hz, 4H, morph-H2/H6), 3.19 (t, *J* = 7.2 Hz, 2H, CO-C$\underline{H_2}$), 2.83 (t, *J* = 7.2 Hz, 2H, C$\underline{H_2}$-N-morph), 2.50 (t, *J* = 4.0 Hz, 4H, morph-H3/H5); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 198.4 (C=O), 150.9 (py-C2/C6), 142.6 (py-

C4), 120.9 (py-C3/C5), 66.8 (morph-C2/C6), 53.6 (morph-C3/C5), 53.0 ($\underline{C}H_2$-N-morph), 36.3 (CO-$\underline{C}H_2$); nmr assignments are based on HMBC and HSQC experiments; esi-hrms: calcd for $[M+H]^+$ $C_{12}H_{17}N_2O_2$ 221.1285; observed 221.1288.

7-Methylisoquinolin-5-ol (18). To a stirred solution of Weinreb's amide **4** (60.0 mg, 0.224 mmol) in dry THF at -78 °C MeMgBr (1.0 mL, 1.0 mmol, 1M in butyl ether) was added dropwise. The reaction was allowed to heat to room temperature and stirred for 2 h. Then EtOAc (10 mL), brine (10 mL) and H_2O (5 mL) was added. After extraction with EtOAc (3 × 10 mL), the combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. An aqueous solution of Na_2CO_3 (15 mL, sat.) was added to the brown oil and the mixture was stirred over night. Extraction with EtOAc (3 × 10 mL), drying over Na_2SO_4, concentration under reduced pressure and flash chromatography (gradient; 2.5 – 5% MeOH/CH_2Cl_2) gave the title compound **18** as a white solid, 20 mg (56%), mp > 215 °C (decomp), pure by nmr; R_f 0.18 (5% MeOH/CH_2Cl_2); ir: 3400-2400br, 1588m, 1396s, 1350m, 1281s, 1037m, 832s cm^{-1}; ^{1}H nmr (400 MHz, DMSO-d_6): δ_H 10.39 (s, 1H, OH), 9.10 (s, 1H, H1), 8.36 (d, J = 5.6 Hz, 1H, H3), 7.84 (d, J = 5.6 Hz, 1H, H4), 7.30 (s, 1H, H8), 6.93 (s, 1H, H6), 2.43 (s, 3H, -CH_3); ^{13}C nmr (100 MHz, DMSO-d_6): δ_C 152.1 (C5), 151.1 (C1), 141.1 (C3), 137.7 (C7), 129.5 (C8a), 125.3 (C4a), 116.6 (C8), 114.8 (C4), 113.9 (C6), 21.6 (-CH_3); nmr assignments are based on HMBC, HSQC and NOESY experiments; esi-hrms: calcd for $[M+H]^+$ $C_{10}H_{10}NO$ 160.0757; observed 160.0759.

1,3-Dimethyl-1H-pyrano[4,3-c]pyridin-1-ol (19). A solution of Weinreb's amide **4** (36 mg, 0.14 mmol) in dry THF (2 mL) was added methylmagnesium bromide (0.4 mL, 0.4 mmol, 1M in butyl ether) dropwise at -78 °C. The reaction mixture was allowed to heat to room temperature and stirred for 3 h before a solution of NH_4Cl (10 mL) was added. The aqueous solution was extracted with diethyl ether (3 × 15 mL). After drying over Na_2SO_4, evaporation of solvent and flash chromatography (2.5% MeOH/CH_2Cl_2), the title compound **19** was obtained as a yellow oil, 15 mg (64%), pure by nmr; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 9.20 (s, 1H, py-H2), 8.63 (d, J = 5.6 1H, py-H6), 7.81 (d, 1H J = 5.6 Hz, py-H5), 7.45 (s, 1H, pyran-C$\underline{H}$=C), 2.94 (s, 3H, CH_3), 2.71 (s, 3H, CH_3); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 158.0 /152.4 / 131.2 / 127.4 (py-C3, -C4, pyran-C1, -C3), 151.9 (py-C2), 143.7 (py-C6), 117.6 (py-C5), 115.5 (pyran-$\underline{C}$H=), 24.4 (Me), 21.7 (Me); nmr assignments are based on HMBC and HSQC experiments; esi-hrms: calcd for $[M+H]^+$-H_2O $C_{10}H_{10}NO$; 160.0757; observed 160.0758.

Preparation of 8, 20 and 21. A solution of Weinreb's amide **4** (355 mg, 1.328 mmol) in dry THF (5 mL) was cooled to -78 °C, and allylmagnesium bromide (3.45 mL, 3.45 mmol, 1M in ether) was added dropwise. The reaction was stirred for 2 h at -78 °C and allowed to heat to room temperature. NH_4Cl (15 mL, sat) was added and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash column chromatography (EtOAc/pentane (1:1)) allowed the isolation of compounds **8**, **20** and **21**.

7-Allyl-6-vinylisoquinolin-5-ol (8). The title compound **8** was obtained as a yellow oil, 31 mg (11%), pure by ^{1}H nmr; R_f 0.26 (EtOAc/pentane (1:1)); ir (KBr): 3074w, 2976w, 2922w, 2800w br, 1623m, 1579s, 1566m, 1394s, 1260s, 1180s, 1038s, 1024m, 921s, 847m cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$):δ_H 9.12 (s, 1H, H1), 8.49 (d, J = 5.6 Hz, 1H, H3), 7.95 (d, J = 5.6 Hz, 1H, H4), 7.35 (s, 1H, H8), 6.84 (dd, J = 18.4, 11.6 Hz, 1H, vinyl; C$\underline{H}$=CH_2), 6.31 (br s, 1H, OH), 6.01 (m, 1H, allyl; C$\underline{H}$=CH_2), 5.88 (dd, J = 11.6, 1.6 Hz, 1H, vinyl; CH=C$\underline{H_a}H_b$), 5.71 (dd, J = 18.4, 1.6 Hz, 1H, vinyl; CH=C$H_a\underline{H_b}$), 5.14 (m, 1H, allyl; CH=C$\underline{H_a}H_b$), 5.04 (m, 1H, allyl; CH=C$H_a\underline{H_b}$), 3.49 (m, 2H, allyl -C$\underline{H_2}$); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C151.3 (C1), 147.3 (C5), 142.2 (C3), 137.8 (C7) 135.8 (allyl; $\underline{C}$H=), 132.1 (vinyl; $\underline{C}$H=), 128.5 (C8a), 125.7 (C4a), 122.4 (vinyl; =$\underline{C}H_2$), 122.2 (C6), 118.5 (C8), 116.8 (allyl; =$\underline{C}H_2$), 115.4 (C4), 38.2 (allyl; $\underline{C}H_2$-); nmr assignments are based on NOESY, HSQC and HMBC experiments; ei-ms: m/z 212 (M^+, 100%).

7-Allyl-6-ethylidene-7-hydroxy-7,8-dihydroisoquinolin-5(6H)-one (20). The title compound **20** was obtained as a red solid 80 mg (26%), pure by ^{1}H nmr; R_f 0.20 (EtOAc/pentane (1:1)); ir (KBr): 3400br, 3074w, 2931w, 1678s, 1615m, 1416s, 1354m, 1247m, 1067m, 917m, 846m, 729m cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.65 (d, J = 5.2 Hz, 1H, H3), 8.60 (s, 1H, H1), 7.84 (d, J = 5.2 Hz, 1H, H4), 6.63 (q, J = 7.2 Hz, 1H, =C$\underline{H}$-CH_3), 5.85-5.73 (m, 1H, C$\underline{H}$=CH_2), 5.19 (m, 1H, allyl =C$\underline{H_a}H_b$), 5.06 (m, 1H, allyl =C$H_a\underline{H_b}$), 3.16 (br s, 1H, H8; C$\underline{H_a}H_b$), 3.15 (br s, 1H, H8; C$H_a\underline{H_b}$), 2.4-2.2 (m, 2H, allyl-CH_2), 2.17 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 188.5 (C=O), 150.9 (C1), 148.7 (C3), 140.9 / 138.7 / 133.3 (C4a, C6, C8a), 137.9 (=C$\underline{H}$-CH_3),132.1 (allyl-C$\underline{H}$=CH_2), 120.4 / 119.6 (C4, allyl =C$\underline{H_2}$), 74.6 (C7), 43.9 (allyl-C$\underline{H_2}$-CH=), 39.7 (C8), 15.8 (=CH-C$\underline{H_3}$); nmr assignments are based on HSQC and HMBC experiments.

1,3-Diallyl-1H-pyrano[4,3-c]pyridin-1-ol (21). The title compound **21** was obtained as a yellow oil, 20 mg (6%), pure by ^{1}H nmr. Product **21** was, correspondingly, obtained in 21% by addition of a pre-cooled NH_4Cl solution to the reaction mixture kept at -78 °C. R_f 0.40 (EtOAc/pentane (1:1)); ir (film): 3404br, 3076w, 2977w, 2918w, 1744w, 1638m, 1618w, 1572s, 1481m, 1427w, 1376w, 1152w, 995m, 915s, 859m cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 9.24 (s, 1H, py-H2), 8.62 (d, J = 6.0 Hz, 1H, py-H6), 7.85 (d, J = 6.0 Hz, 1H, py-H5), 7.49 (s, 1H, pyrano-H4), 6.2-6.1 (m, 2H, 2 × allyl C$\underline{H}$=CH_2), 5.25-5.15 (m, 4H, 2 × allyl CH=C$\underline{H_2}$), 4.07 (m, 2H, 1-pyrano-allyl; CH(OH)-C$\underline{H_a}H_b$-CH=), 3.77 (m, 2H, 3-pyrano-allyl; =C-C$\underline{H_a}H_b$=CH); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 159.2 /154.6 /131.5 /127.4 (py-C3, -C4, pyran-C1, -C3), 152.3 (py-C2), 143.9 (py-C6), 135.5 / 135.0 (2

× allyl -CH=), 117.4 (py-C5), 117.2 / 117.1 (2 × allyl=$\underline{C}H_2$), 115.5 (pyran-$\underline{C}H$=C), 42.5 (3-pyran-allyl; =C-$\underline{C}H_2$-CH=), 39.9 (1-pyran-allyl; CH(OH)-$\underline{C}H_2$-CH=); nmr assignments are based on HSQC and HMBC experiments.

Formation of 8 by isomerisation of 20. An nmr sample of **20** (10 mg) in $CDCl_3$ was added crystalline *p*-TsOH (2 mg) and left at room temperature. The isomerisation was monitored by ^{1}H nmr and tlc. Full conversion of **20** into **8**, pure by ^{1}H nmr, was obtained after 10 h.

7-Allyl-6-(1-methoxyethyl)isoquinolin-5-ol (20'). A sample of **20** (20 mg, 0.08 mmol) in MeOH (5 mL) was added crystalline NaOMe (approx 30 mg) and stirred over night at room temperature. Quenching with an NH_4Cl solution (15 mL), extraction with EtOAc (3 × 20 mL), drying over Na_2SO_4 and evaporation of solvent afforded product **20'** (20 mg, 98%), pure by nmr; ir (film): 3271br, 2928s, 1635m, 1581s, 1462m, 1403s, 1286m, 1109m cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$); δ_H 9.26 (br s, OH), 9.15 (s, 1H, H1), 8.50 (br s, 1H, H3), 8.00 (br s, 1H, H4); 7.29 (s, 1H, H8), 6.0-6.1 (m, 1H, allyl-CH=), 5.17 (dd, *J* = 10.4, 1.6 Hz, 1H, allyl=C$\underline{H}_a$H$_b$), (d, *J* = 17.2, 1.6 Hz, 1H, allyl-CH$_a$$\underline{H}_b$), 4.91 (q, *J* = 6.8 Hz, 1H, C$\underline{H}$-OMe), 3.48 (d, *J* = 5.6 Hz, 2H, allyl-CH_2), 3.41 (s, 3H, OMe), 1.58 (d, *J* = 6.8 Hz, 1H, CH-$\underline{Me}$); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 150.9 (C1), 141.9 (C3), 136.5 (allyl-CH=), 151,2 / 136.6 / 129.0 / 127.2 / 122.6 (C4a, C5, C6, C7, C8a), 119.2 (C8), 116.9 (allyl=CH_2), 115.1 (C4), 78.0 ($\underline{C}$H-OMe), 57.4 (OMe), 37.4 (allyl-CH_2-), 20.8 (Me); nmr assignments are based on HSQC and HMBC experiments.

Preparation of 22, 23 and 24. A solution of diester **3** (300 mg, 1.44 mmol) and Me(MeO)NH·HCl (330 mg, 3.3 mmol) in dry THF (30 ml) at -5 °C was added allylMgCl (6 mL, 12 mmol, 2 M in THF) over 2 h. The reaction mixture was kept stirring for 20 h, and then HCl (10 ml, 10%) was added. pH 9 was obtained by addition of a $NaHCO_3$ solution. The products **22** (94 mg, 26%), **23** (12 mg, 3%) and **24** (108 mg, 24%) were isolated by extraction and flash chromatography (EtOAc/pentane (1:6)). Correspondingly, only product **22** (32%) was isolated from an experiment carried out at -15 °C for only 2 h, using **3** (200 mg, 0.95 mmol), Me(MeO)NH·HCl (220 mg, 2.2 mmol) and allylMgCl (1.1 mL, 2.2 mmol, 2 M in THF) in dry THF (30 ml).

1-(3-(2-Allylpenta-1,4-dienyl)pyridin-4-yl)but-3-en-1-one (22). ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.31 (d, *J* = 5.2 Hz, 1H, py-H6), 8.15 (s, 1H, py-H2), 6.81 (d, *J* = 5.2 Hz, 1H, py-H5), 5.88 (m, 1H, C$\underline{H}$=CH$_2$), 5.72 (m, 1H, 4-py-side-chain; C$\underline{H}$=CH$_2$), 5.52 (s, 2H, 3-py-side-chain; 2 × CH=C), 5.20 (m, 1H, 4-py-side-chain; =CH$\underline{H}$), 5.16 (m, 1H, 4-py-side-chain; =CH$\underline{H}$), 5.07 (m, 2H, 3-py-side-chain; =CH$\underline{H}$), 5.06 (m, 1H, 3-py-side-chain; =CH$\underline{H}$), 5.03 (m, 1H, 3-py-side-chain; =CH$\underline{H}$), 2.92 (dd, *J* = 6.0, 1.2 Hz, 2H, 4-py-side-chain; C-CH_2), 2.65 (dd, *J* = 7.2, 1.0 Hz, 4H, 3-py-side-chain; 2 × C-CH_2); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 156.2 (C=O), 148.3 (py-C6), 144.9 (py-C2), 140.1 (py-C4), 133.4 (4-py-side-chain; $\underline{C}$H=C), 133.2 (3-py-side-chain; 2 × $\underline{C}$H=C), 127.8 (py-C3), 120.1 (py-C5), 119.3 (3-py-side-chain; 2 × $\underline{C}H_2$=C), 118.5 (4-py-side-chain; $\underline{C}H_2$=C), 96.3 (3-py-$\underline{C}$H=), 81.8 (3-py-CH=$\underline{C}$), 42.6 (3-py-side-chain; 2 × $\underline{C}H_2$-CH=CH$_2$), 38.8 (4-py-side-chain; $\underline{C}H_2$-CH=CH$_2$); nmr assignments are based on APT, HMBC, HSQC experiments; ei-ms: m/z 253 (M$^+$, 4%), 212 (100), 193 (9), 170 (14), 167 (9), 154 (8), 142 (33), 130 (8), 115 (17); ei-hrms: calcd for $C_{17}H_{19}NO$; 253.1467; observed 253.1469.

1-(2-allyl-3-(2-allylpenta-1,4-dienyl)pyridin-4-yl)but-3-en-1-one (23). ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.27 (d, *J* = 4.8 Hz, 1H, py-H6), 6.72 (d, *J* = 4.8 Hz, 1H, py-H5), 6.04 (m, 1H, C$\underline{H}$=CH$_2$), 5.90 (m, 1H, C$\underline{H}$=CH$_2$), 5.73 (m, 2H, 2 × C$\underline{H}$=CH$_2$), 5.60 (s, 1H, 3-py-CH=C), 5.22 (m, 1H, =CH$\underline{H}$), 5.17 (m, 1H, =CH$\underline{H}$), 5.13 (m, 1H, =CH$\underline{H}$), 5.09 (m, 1H, =CH$\underline{H}$), 5.07 (m, 2H, 2 × =CH$\underline{H}$), 5.04 (m, 1H, =CH$\underline{H}$), 5.02 (m, 1H, =CH$\underline{H}$), 3.56 (d, *J* = 7.0 Hz, 2H, 4-py-side-chain, C-CH_2), 2.94 (d, *J* = 6.0 Hz, 2H, 2-py-side-chain, C-CH_2), 2.64 (d, *J* = 8.0 Hz, 4H, 3-py-side-chain; 2 × C-CH_2); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 155.6 (C=O), 152.1 (py-C2), 146.3 (py-C6), 139.9 (py-C4), 135.6 (4-py-side-chain; $\underline{C}$H=C), 133.2 (2-py-side-chain; $\underline{C}$H=C), 129.8 (3-py-side-chain; 2 × $\underline{C}$H=C), 125.3 (py-C3), 119.3 (3-py-side-chain; 2 × $\underline{C}H_2$=C), 118.5 (py-C5), 118.4 (2-py-side-chain; $\underline{C}H_2$=C), 118.4 (4-py-side-chain; $\underline{C}H_2$=C), 96.5 (3-py-$\underline{C}$H=), 81.6 (3-py-CH=$\underline{C}$), 42.4 (3-py-side-chain; 2 × $\underline{C}H_2$-CH=CH$_2$), 38.8 and 39.2 (2- and 4-py-side-chain; $\underline{C}H_2$-CH=CH$_2$); nmr assignments are based on HMBC experiments; ei-ms: m/z 293 (M$^+$, 3%), 268 (2), 252 (100), 234 (3), 210 (5), 167 (9), 154 (5); ei-hrms: calcd for $C_{20}H_{23}NO$; 293.1780; observed 293.1764.

4-(3-(2-allyl-2-hydroxypent-4-enyl)pyridin-4-yl)hepta-1,6-dien-4-ol (24). ir: 3346m, 3000s (br), 3071w, 2976w, 2924w, 2840w 1640s, 1598s, 1490w, 1438s, 1405s, 1270s, 1150m, 1075m, 1045s, 987s, 912s, 845m cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 8.36 (d, *J* = 5.2 Hz, 1H, py-H6), 8.27 (s, 1H, py-H2), 7.06 (d, *J* = 5.2 Hz, 1H, py-H5), 5.86 (m, 2H, 3-py-side-chain; 2 × C$\underline{H}$=CH$_2$), 5.68 (m, 2H, 4-py side-chain; 2 × C$\underline{H}$=CH$_2$), 5.38 (s, br, 1H, 3-py side-chain; OH), 5.21 (m, 1H, 3-py-side-chain; =CH$\underline{H}$), 5.19 (m, 1H, 3-py-side-chain; =CH$\underline{H}$), 5.18 (m, 1H, 3-py-side-chain; =CH$\underline{H}$), 5.16 (m, 1H, 3-py-side-chain; =CH$\underline{H}$), 5.02 (m, 2H, 4-py side-chain; 2 × =CH$\underline{H}$), 5.00 (m, 1H, 4-py-side-chain; =CH$\underline{H}$), 4.98 (m, 1H, 4-py-side-chain; =CH$\underline{H}$), 3.26 (s, 2H, 3-py-CH_2), 2.77 (s, br, 1H, 4-py side-chain; OH), 2.65 (dd, *J* = 14.0, 7.2 Hz, 2H, 4-py side-chain; 2 × CH$\underline{H}$), 2.54 (dd, *J* = 14.0, 7.6 Hz, 2H, 4-py side-chain; 2 × CH$\underline{H}$), 2.38 (dd, *J* = 14.0, 7.2 Hz, 2H, 3-py side-chain; 2 × CH$\underline{H}$), 2.23 (dd, *J* = 14.0, 7.6 Hz, 2H, 3-py side-chain; 2 × CH$\underline{H}$); ^{13}C nmr (100 MHz, $CDCl_3$): δ_C 155.1 (py-C2), 154.4 (py-C4), 147.5 (py-C6), 133.4 (4-py-side-chain; 2 × $\underline{C}$H=C), 133.2 (3-py-side-chain; 2 × $\underline{C}$H=C), 131.0 (py-C3), 122.6 (py-C5), 119.9 (3-py-side-chain; 2 × $\underline{C}H_2$=C), 119.0 (4-py-side-chain; 2 × $\underline{C}H_2$=C), 78.4 (4-py-$\underline{C}$-OH), 73.8 (3-py-CH$_2$-$\underline{C}$-OH), 48.1 (3-py-side-chain; 2 × $\underline{C}H_2$-CH=CH$_2$), 43.9 (4-py-side-chain; 2 × $\underline{C}H_2$-

$CH=CH_2$), 39.6 (3-py-$\underline{C}H_2$); nmr assignments are based on APT, HMBC, HSQC experiments and D_2O exchange; ms: m/z 313 (M^+, 22%), 273 (8), 246 (10), 186 (57), 171 (18), 157 (29), 127 (31), 125 (83), 91 (34), 44 (100).

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